Annual Meeting & Best of ASCO®

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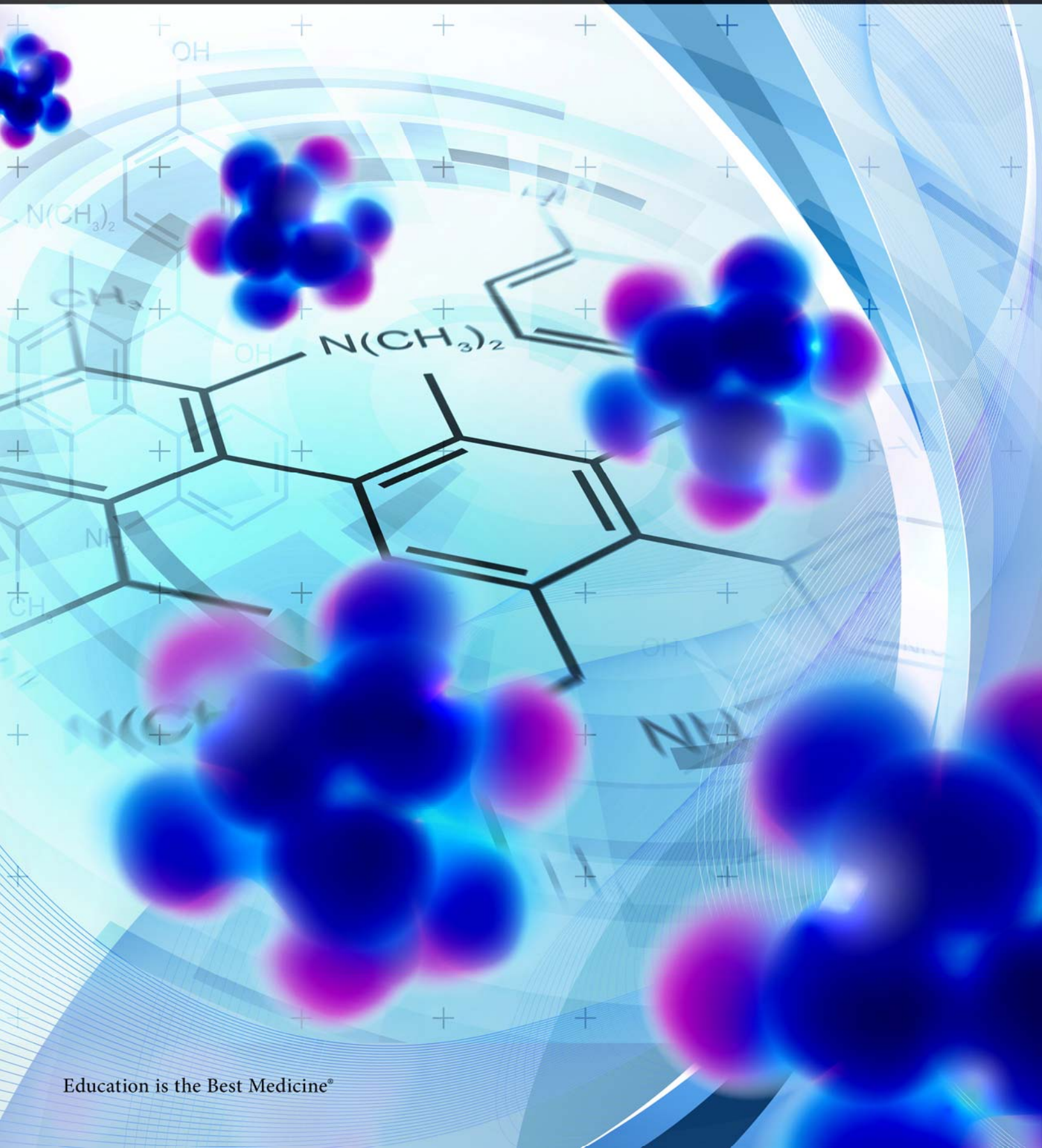
GASCO

September 6 - 7, 2013
Atlanta, Georgia
Intercontinental Hotel, Buckhead



Education is the Best Medicine®

AGENDA September 6, 2013

12:00 PM	Registration & Exhibits Open
1:00 PM	Welcome and Introductions *Hillary Hahm, M.D. – GASCO President* *Rodolfo Bodoni, M.D. – Program Co-Chair*
1:15 AM	Clinical Think Tank – Optimization of Diagnosis and Treatment of Advanced Lung Cancer in the Era of Molecular Oncology Case 1 & Moderator Introduction *Rudolfo Bordoni, M.D*
1:30 PM	Potential Therapeutic Strategies for Genetically Defined NSCLC Subsets (*Panel Discussion & Questions to Follow)* *Vincent Miller, M.D. – Foundation Medicine*
2:00 PM	Break & Poster Displays – Exhibitor Area
2:30 PM	*Case 1 & Moderator Introduction* *Rudolfo Bordoni, M.D*
3:00 PM	Treatment Algorithms in Tumors with No Actionable Tumor Markers (*Panel Discussion & Questions to Follow)* *Suresh Ramalingam, M.D. – Winship Cancer Institute of Emory University*
4:00 PM	Address from Richard L. Shilsky, *M.D., Chairman, ASCO Government Relations Committee*
5:15 PM	President's Reception for Faculty Conference Participants Sponsors & Guests
5:45 PM	Dinner
6:00 PM	**"Oncology Exchange: Emerging Strategies in the Management of Multiple Myeloma"** Sagar Lonial, M.D. - *Winship Institute of Emory University*
7:00 PM	Closing Comments & Adjourn

AGENDA September 7, 2013

7:00 AM Breakfast & Registration

8:00 AM Welcome and Introduction
Ruth M. O'Regan, M.D. – Program Co-Chair
Rodolfo Bordoni, M.D. – Program Co-chair

8:15 AM Breast Cancers
Ruth O'Regan, M.D.

Abstract Presentations and Questions

9:15 AM Break and Poster Displays – Exhibit Area

9:45 AM Lung Cancers/Head & Neck
Fadlo R. Khuri, M.D.

10:45 AM Gynecology/Oncology
Sharad Ghamande, M.D.

Abstract Presentations and Questions

11:45 AM Lunch Presentations
- *Best Poster Submission*
- *Mumber Visionary Award for Patient Navigation*
- *Lung Cancer Screening and Prevention Toolkit Presentation*

1:00 PM Gastrointestinal Cancers
Bassel El-Rayes, M.D.

Abstract Presentations and Questions

2:00 PM Genitourinary Cancers
Guru Sonpavde, M.D.

Abstract Presentations and Questions

3:00 PM Break

3:30 PM Central Nervous Track
Oliver Rixe, M.D.
Thyroid Cancers
Taefeek Owonikoko, M.D.
Melanoma
David Lawson, M.D.

Abstract Presentations and Questions

4:30 PM Closing Remarks and Adjourn
Hillary Hahm, M.D.,
GASCO President

Faculty

Speakers for Friday September 6, 2013

Rudofo Bordoni, M.D.
Georgia Cancer Specialists
Atlanta, Georgia

Vincent Miller, M.D.
Senior Vice President, Clinical Development
Foundation Medicine
Cambridge, Massachusetts

Sagar Lonial, M.D.
Winship Cancer Institute
Emory University
Atlanta, Georgia

Suresh Ramalingam, M.D.
Winship Cancer Institute
Emory University
Atlanta, Georgia

Richard Shilsky, M.D.
Chairman, ASCO Government Relations Committee
University of Chicago

Best of ASCO – September 7, 2013

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Atlanta, Georgia

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Credit Statement

Accreditation

The Medical College of Georgia at Georgia Regents University is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation

The Medical College of Georgia at Georgia Regents University designates this live activity for a maximum of 13.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CEUs

This activity includes 13.25 hours of instruction and attendance at the entire activity is approved by Georgia Regents University for a maximum of 1.325 Continuing Education Credit Units.

TABLE OF CONTENTS

Publication Information: In our continuing effort to provide conference attendees with a permanent copy of the information discussed at this meeting, a summary and/or presentation have been requested from the speakers at this meeting. All available slides are at www.gasco.us/meeting-slides.php. While every effort has been made to secure this information, in some cases these requests are not fulfilled by a speaker for a variety of reasons. We appreciate your understanding in our quest to provide you with the most updated and complete information possible, and are confident that you will have an enjoyable and educational experience.

American Society of Clinical Oncology

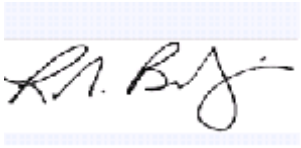
July 29, 2013

The American Society of Clinical Oncology (ASCO®) is pleased to announce an agreement with the Georgia Society of Clinical Oncology to hold an official Best of ASCO® meeting in Atlanta, GA on September 6-7, 2013. This premier event will highlight abstracts and educational updates from the 2013 ASCO Annual Meeting, the world's largest gathering of physicians, researchers, and others engaged in the study and practice of oncology.

Many summary events are held after the Annual Meeting, but only a select few are organized in connection with ASCO and reliably deserve the title "Best of ASCO" for their objectivity in content selection. These official Best of ASCO meetings present the top abstracts from a pool of more than 4,000 rated by a panel of ASCO experts. The Georgia Society of Clinical Oncology has created a custom program that promises to meet the needs of members of the oncology care team.

ASCO would like to take this opportunity to encourage you to support official Best of ASCO meetings, including the one being held in Atlanta on September 6-7, 2013. Best of ASCO meetings are an excellent way to support local physicians with the latest science and education.

Sincerely,



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BREAST CANCER

Ruth O' Regan, M.D.

NOTES

Abstract: 500

Title: Clinical and translational results of CALGB 40601: A neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for HER2-positive breast cancer.
Track: Breast Cancer, HER2/ER

Authors: Lisa A. Carey, Donald A. Berry, David Ollila, Lyndsay Harris, Ian E. Krop, Douglas Weckstein, Norah Lynn Henry, Carey K. Anders, Constance Cirrincione, Eric P. Winer, Charles M. Perou, Clifford Hudis, Alliance; The University of North Carolina at Chapel Hill, Chapel Hill, NC; The University of Texas MD Anderson Cancer Center, Houston, TX; Case Western/Seidman Cancer Center, Cleveland, OH; Dana-Farber Cancer Institute, Boston, MA; New Hampshire Oncology-Hematology, PA, Hooksett, NH; University of Michigan Medical Center, Ann Arbor, MI; The University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Alliance Statistical Center, Duke University, Durham, NC; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Recent trials in HER2-positive (HER2+) breast cancer (BrCa) demonstrate increased pathological complete response (pCR) using dual HER2-targeting in the neoadjuvant setting and increased progression-free survival in metastatic disease. CALGB 40601 aimed to further quantify the pCR rates of weekly paclitaxel (T) and trastuzumab (H) alone or combined HER2-blockade of H with the small molecule lapatinib (L), and to identify biomarkers of sensitivity to these HER2-targeted agents. **Methods:** Eligible patients had newly diagnosed, noninflammatory stage II-III HER2+ BrCa and were randomized to receive T (80mg/m2/week IV) + H (4mg/kg then 2mg/kg/week IV) alone (TH) or with the addition of L (750 mg/d PO) (THL) for 16 weeks preoperatively. A third arm, T + L (1500 mg/d) (TL), was closed early when negative efficacy and toxicity data emerged from preliminary analysis of ALTTO. After surgery, 4 cycles of adjuvant dose-dense AC and 1 year H was recommended. Tumors were biopsied for research before therapy; post-Rx samples of residual disease were requested. The primary endpoint was in-breast pCR rate; the study had 85% power to detect an increase from 30% (TH) to 50% (THL). **Results:** 305 patients were randomized (118 THL, 120 TH, 67 TL); 68% were clinical stage II and 59% hormone receptor-positive. Grade 3+ toxicity was higher among L-containing arms, including neutropenia (12% TL, 7% THL, 2% TH), rash (15% TL, 14% THL, 2% TH), and diarrhea (20% TL, 20% THL, 2% TH). Breast pCR rates with 95% confidence limits were: 51% (42-60%) THL, 40% (32-49%) TH, 32% (22-44%) TL. pCR rate in the TH arm was higher than previous studies, and was not significantly different from THL (p=0.11). We will present molecular subtype, sequence and gene copy number abnormalities in primary tumors and residual disease. **Conclusions:** pCR rate was higher with combined THL compared with standard TH but did not reach statistical significance. These results are qualitatively similar to other neoadjuvant studies in HER2+ BrCa, and contribute to estimates of pCR rates after these agents. Tissue-based studies may illuminate which patients benefit from HER2-targeting using these agents.
Clinical trial information: NCT00770809.

Abstract: 502

Title: ACOSOG Z1041 (Alliance): Definitive analysis of randomized neoadjuvant trial comparing FEC followed by paclitaxel plus trastuzumab (FEC → P+T) with paclitaxel plus trastuzumab followed by FEC plus trastuzumab (P+T → FEC+T) in HER2+ operable breast cancer.

Track: Breast Cancer – HER2/ER

Authors: Aman Buzdar, Vera J. Suman, Funda Meric-Bernstam, A. Marilyn Leitch, Matthew James Ellis, Judy Caroline Boughey, Gary Walter Unzeitig, Melanie Royce, Kelly Hunt, for the Alliance for Clinical Trials in Oncology; The University of Texas MD Anderson Cancer Center, Houston, TX; ACOSOG Statistical Center, Mayo Clinic, Rochester, MN; Simmons Cancer Center, The University of Texas Southwestern Medical Center, Dallas, TX; Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Mayo Clinic, Rochester, MN; Doctors Hospital of Laredo, Laredo, TX; University of New Mexico Cancer Center, Albuquerque, NM

Background: Neoadjuvant chemotherapy (NAC) and concomitant trastuzumab (T) have produced high pathologic complete response (pCR) rates in HER2+ breast cancers. Z1041 addresses the timing of initiation of T with NAC. **Methods:** Women with operable HER2+ invasive breast cancer were randomized 1:1 to: FEC → P+T (Arm 1) or P+T → FEC+T (Arm 2) where treatment was administered as 5-FU 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 day 1 of a 21-day cycle x 4 (FEC); paclitaxel 80 mg/m^2 weekly x 12 and trastuzumab 4 mg/kg once then 2 mg/kg weekly x 11. Eligibility also included: tumor > 2 cm or a positive lymph node and left ventricular ejection fraction > 55%. The primary aim was to compare the pCR rates in the breast (pBCR) between the regimens. Secondary endpoints were pCR rate in the breast and lymph nodes (pBNCR) and safety profile. All pts who began study treatment were included in the analyses. With 128 pts per regimen, a two-sided alpha=0.05 test of proportions would have a 90% chance of detecting a difference of 20% or more in the pBCR rates, when the pBCR rate with the poorer regimen is ≤ 25%. **Results:** From September 15, 2007 to December 15, 2011, 282 women (Arm 1: 140 pts) were enrolled. Two pts (Arm 1) withdrew without receiving treatment. The two arms were similar in age, stage, and hormone receptor (HR) status (HR neg: 40%). The severe (grade 3+) treatment-related toxicities included: neutropenia (Arm 1: 24.6%; Arm 2: 32.4%), fatigue (Arm 1: 4.3%; Arm 2: 8.5%), and neurosensory problems (Arm 1: 3.6%; Arm 2: 4.9%). The pBCR rate and pBNCR rates (Table) were not found to differ between the two regimens (Fisher's exact p values: 0.905 and 0.811, respectively). **Conclusions:** High pCR rates can be achieved with trastuzumab in combination with anthracyclines and taxanes. The pBCR or pBNCR was not different between regimens based on the timing of initiation of trastuzumab. Clinical trial information: NCT00513292.

Abstract: 505

Title: Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3).

Track: Oral Abstract Session, Breast Cancer - HER2/ER

Authors: Ruth O'Regan, Mustafa Ozguroglu, Fabrice Andre, Masakazu Toi, Guy Heinrich Maria Jerusalem, Sharon Wilks, Claudine Isaacs, Binghe Xu, Norikazu Masuda, Francis P. Arena, Denise Aysel Yardley, Yoon Sim Yap, Pabak Mukhopadhyay, Shyanne Douma, Mona El-Hashimy, Tanya Taran, Tarek Sahmoud, David Edward Lebwohl, Luca Gianni; Georgia Cancer Center for Excellence at Grady Memorial Hospital, Atlanta, GA; Istanbul University, Istanbul, Turkey; Institut Gustave Roussy, Villejuif, France; Graduate School of Medicine Kyoto University, Kyoto, Japan; Centre Hospitalier Universitaire Sart Tilman Liege and University of Liege, Liège, Belgium; Cancer Care Centers of South Texas, San Antonio, TX; Lombardi Comprehensive Cancer Center, Washington, DC; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; NHO Osaka National Hospital, Osaka, Japan; Arena Oncology Associates, Lake Success, NY; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; National Cancer Centre Singapore, Singapore, Singapore; Novartis Pharmaceuticals Corp, East Hanover, NJ; Novartis Pharmaceuticals, East Hanover, NJ; Novartis Pharmaceuticals, Florham Park, NJ; Global Oncology Development, Novartis Pharmaceuticals Corporation, Florham Park, NJ; San Raffaele Scientific Institute, Milan, Italy

Background: Everolimus (EVE) is an inhibitor of mammalian target of rapamycin (mTOR), a protein kinase central to a number of signaling pathways regulating cell growth and proliferation. Data from preclinical and phase 1/2 clinical studies indicated that adding EVE to trastuzumab (TRAS) plus chemotherapy may restore sensitivity to and enhance efficacy of human epidermal growth factor receptor 2 (HER2)-targeted therapy. The international BOLERO-3 phase 3 study is being conducted to evaluate the addition of EVE to TRAS plus vinorelbine. **Methods:** Adult women with $HER2^{+}$ advanced breast cancer and who received prior taxane therapy and experienced recurrence or progression on TRAS were randomized 1:1 to receive either EVE or placebo (5 mg/day) in combination with weekly TRAS and vinorelbine (25 mg/m^2). The primary endpoint is progression-free survival (PFS). Secondary endpoints included overall survival, response rate, clinical benefit rate, safety, quality of life, and pharmacokinetics. Final analysis will be conducted after approximately 417 PFS events. **Results:** The trial accrued 569 patients between October 2009 and May 2012. Previous therapy included TRAS (100%), a taxane (100%), and lapatinib (28%). The median age was 54 years, and 76% of patients had visceral metastases, 5% had stable brain metastases, 56% had hormone-receptor–positive disease, 33% had Eastern Cooperative Oncology Group performance status of 1 or 2, and 41% had 3 or more metastatic sites. The median number of prior chemotherapy lines in the metastatic setting was 1. As of February 4, 2013, a total of 396 PFS events were reported. **Conclusions:** Final PFS analysis will be performed in early May 2013; primary and secondary efficacy endpoints will be presented. Clinical trial information: NCT01007942.

Abstract: 507

Title: Prognostic impact of the 21-gene recurrence score in patients presenting with stage IV breast cancer.

Track: Oral Abstract Session, Breast Cancer - HER2/ER

Authors: Tari A. King, Jaclyn P Lyman, Mithat Gonen, Amy Voci, Marina De Brot, Camilla Boafa, Amy Pratt Sing, Eun-Sil Shelley Hwang, Michael Alvarado, Minetta C. Liu, Judy Caroline Boughey, Kandace P. McGuire, Catherine H. Van Poznak, Lisa K. Jacobs, Ingrid M. Meszoely, Helen Krontiras, Gildy Babiera, Larry Norton, Monica Morrow, Clifford Hudis, Translational Breast Cancer Research Consortium; Department of Surgery, Breast Service, Memorial Sloan-Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Epidemiology-Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Genomic Health, Inc., Redwood City, CA; Duke Unversity Medical Center, Durham, NC; University of California, San Francisco, San Francisco, CA; Mayo Clinic, Rochester, MN; Department of Surgery, Division of Surgical Oncology, Magee-Womens Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Vanderbilt-Ingram Cancer Center, Nashville, TN; University of Alabama at Birmingham, Birmingham, AL; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The 21-gene Recurrence Score (Onco*type*DX Breast Cancer Assay) predicts outcome and benefit from chemotherapy (CT) in early stage ER+ BC treated with adjuvant endocrine therapy. We evaluated the association between Recurrence Score (RS), time to progression (TTP), and overall survival (OS) in patients with stage IV BC enrolled in TBCRC 013. **Methods:** TBCRC 013 is a registry study evaluating surgery of the primary tumor in pts presenting with Stage IV BC. From 7/09 - 4/12, 128 evaluable pts were enrolled in two cohorts (A: metastases (mets) with intact primary tumor (n=112); B: mets within 3 months of primary surgery (n=16)). This study includes 110 pts with pre-treatment primary tumor samples available for analysis. Clinical variables, TTP and OS were correlated with RS using long-rank, Kaplan-Meier and Cox regression. **Results:** Median pt age was 52yrs (21-79) and median tumor size 3.1cm (0.7-15). 82 (80%) were ER+, 83 (81%) Her2(-) and 51 (46%) had bone-only mets. Cohorts A and B did not differ. At a median follow-up of 26 mos (1-47), median TTP is 19 mos (95%CI16-25) and surgery is not associated with OS. 102 samples qualified for RS. 23 (23%) had low RS<18, 29 (28%) intermediate RS, 18-30; and 50 (49%) high RS≥31. Age, tumor size or site of 1stmets was not associated with RS. Risk groups were prognostic for TTP in ER+ pts and for 2 yr OS in ER+Her2- pts (Table). In Cox models continuous RS was also prognostic for TTP in ER+ pts (HR 3.5; for 50 point difference (PD) 95%CI 1.5-8.1, p=0.003) and for OS in ER+Her2- pts (HR 21.4, for 50 PD 95%CI 2.2-204.4, p=0.008). In MVA, adjusting for clinical variables, RS remained prognostic for TTP in ER+ pts (p=0.01). Further analysis of surgery in this trial is ongoing. **Conclusions:** The 21-gene RS is independently prognostic for TTP in ER+ Stage IV BC. RS is also prognostic for OS in ER+Her2- BC, suggesting that a high RS may be a surrogate for endocrine resistance and could be used to select pts with ER+ Stage IV BC for CT. A randomized trial to address this hypothesis is warranted. Clinical trial information: NCT00941759.

Abstract: 1003

Title: PrECOG 0105: Final efficacy results from a phase II study of gemcitabine (G) and carboplatin (C) plus iniparib (BSI-201) as neoadjuvant therapy for triple-negative (TN) and BRCA1/2 mutation-associated breast cancer.

Track: Oral Abstract Session, Breast Cancer - Triple-Negative/Cytotoxics/Local Therapy

Authors: Melinda L. Telli, Kristin C. Jensen, Allison W. Kurian, Shaveta Vinayak, Jafi A. Lipson, Elizabeth A. Schackmann, Irene Wapnir, Robert W. Carlson, Joseph A. Sparano, Bobbie Head, Lori J. Goldstein, Barbara B. Haley, Shaker R. Dakhil, Judith Manola, James M. Ford; Stanford University, Stanford, CA; Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY; California Cancer Care, Greenbrae, CA; Fox Chase Cancer Center, Philadelphia, PA; University of Texas Southwestern, Dallas, TX; Cancer Center of Kansas, Wichita, KS; PrECOG, Philadelphia, PA

Background: TN and BRCA1-deficient breast cancer (BC) cell lines exhibit enhanced sensitivity to DNA damaging agents. This study was designed to assess efficacy, safety and predictors of response to iniparib in combination with GC in early-stage TN and BRCA1/2 mutation-associated BC. **Methods**: This single-arm, phase II study (NCT00813956) enrolled pts with clinical stage I-IIIA (T ≥ 1cm by MRI) ER-negative (≤ 5%), PR-negative (≤ 5%), and HER2-negative or BRCA1/2 mutation-associated BC. Neoadjuvant G (1000 mg/m^2; IV; D1, 8), C (AUC 2; IV; D1, 8), and iniparib (5.6 mg/kg; IV; D1, 4, 8, 11) were given every 21 days for 4 cycles, until the protocol was amended to increase the treatment duration to 6 cycles, with enrollment of 80 pts at multiple PrECOG institutions. The primary endpoint is pathologic complete response (pCR), defined as no invasive carcinoma in the breast and axilla. Pathologic response was centrally assessed by the residual cancer burden (RCB) index. Assuming 76/80 eligible and treated pts, the regimen would be deemed effective if the lower bound of a 90% exact binomial CI on the pCR rate exceeded 25%. Secondary endpoints are safety, MRI response, and breast conservation. **Results**: Among 80 eligible pts treated with 6 cycles, median age is 48 years, 19 pts have germline BRCA1/2 mutations (90% tested to date) and clinical stage is I (13%), IIA (36%), IIB (36%), IIIA (15%). Pathologic response data (ITT population) are detailed below. 69 pts completed treatment per protocol: 5 progressed, 5 discontinued due to an AE and 1 mutation carrier was lost to follow-up. Most common G3/4 adverse events are neutropenia (49%), elevated ALT/AST (14%), and anemia (10%). **Conclusions**: Preoperative GC plus iniparib is active in the treatment of early-stage TN and BRCA1/2 mutation-associated BC. Clinical trial information: NCT00813956.

Abstract: 1004

Title: A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto).

Track: Oral Abstract Session, Breast Cancer - Triple-Negative/Cytotoxics/Local Therapy

Authors: Gunter Von Minckwitz, Andreas Schneeweiss, Christoph Salat, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens U. Blohmer, Hans Tesch, Fariba Khandan, Sebastian Jud, Christian Jackisch, Keyur Mehta, Sibylle Loibl, Michael Untch, German Breast Group; German Breast Group, Neu-Isenburg, Germany; National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany; Hematology Oncology Clinic, Munich, Germany; Breast Center Duesseldorf, Louis Hospital, Düsseldorf, Germany; Frauenklinik Gera, Gera, Germany; Praxisklinik Krebsheilkunde, Berlin, Germany; Brustzentrum Sankt-Gertrauden-Krankenhaus, Berlin, Germany; Onkologische Gemeinschaftspraxis am Bethanien-Krankenhaus, Frankfurt/Main, Germany; Frauenklinik, St. Markus Krankenhaus, Frankfurt, Germany; Frauenklinik, Universitätsklinikum, Erlangen, Germany; Klinikum Offenbach, Offenbach, Germany; Helios Klinikum Berlin-Buch, Berlin, Germany

Background: Use of carboplatin in neoadjuvant chemotherapy (NACT) has never been prospectively examined in breast cancer. Cohort studies suggest a high sensitivity to DNA-damaging agents (e.g., carboplatin in triple negative breast cancer [TNBC]), which have a high prevalence of BRCA mutations. Two trials examining carboplatin in HER2+ metastatic disease have shown conflicting results, but one was biased by different dosage of docetaxel in treatment arms. GeparSixto investigates the impact of carboplatin in addition to an identical, optimized cytotoxic-targeted regimen on pathological complete response (pCR) in these two breast cancer subtypes. **Methods:** In GeparSixto trial (NCT01426880) patients were treated for 18 weeks with paclitaxel 80mg/m² q1w and non-pegylated-liposomal doxorubicin (NPLD) 20mg/m² q1w. HER2+ patients received concurrently trastuzumab 6(8) mg/kg q3w and lapatinib 750mg daily. TNBC patients received concurrently Bevacizumab 15mg/kg i.v. q2w. All patients were randomized 1:1 to receive concurrently carboplatin AUC 1.5-2 q1w vs not, stratified by subtype. Primary objective is pCR rates (ypT0 ypN0), secondary objectives are pCR rate in predefined subgroups or by other definitions, clinical response rate, compliance and tolerability of carboplatin. Carboplatin dose was reduced from AUC 2.0 to 1.5 by an amendment after 330 patients due to carboplatin-related toxicity at pre-planned safety analyses. **Results:** 595 patients were recruited (8/2011 - 12/2012) in 51 German centers, 299 did not receive carboplatin. Median age was 47/48 years (no carb/carb), 36.8/36.5% were postmenopausal; 14.0/13.3% had T3, 5.0/3.7% T4, 41.8/37.6% N+, 93.0/92.9% ductal invasive, 64.5/65.3% G3 tumors; 46.2/46.3% had HER2+, 53.8/53.7% TNBC. 225 patients had a SAE (149 no carb/177 carb) and 3 died (postoperative pneumonia; reduced general condition; acute myocardial infarct), all in no carb arms. Final analysis on primary endpoint will be presented. **Conclusions:** This is first study, evaluating efficacy and safety of the addition of carboplatin to anthracycline-taxane containing NACT in patients with primary HER2+ and TNBC. Clinical trial information: NCT 01426880.

Abstract: 1007

Title: Comparison of doxorubicin and cyclophosphamide (AC) versus single-agent paclitaxel (T) as adjuvant therapy for breast cancer in women with 0-3 positive axillary nodes: CALGB 40101.

Track: Oral Abstract Session, Breast Cancer - Triple-Negative/Cytotoxics/Local Therapy

Authors: Lawrence N. Shulman, Donald A. Berry, Constance T. Cirrincione, Heather Becker, Edith A. Perez, Ruth O'Regan, Silvana Martino, Charles L. Shapiro, James Atkins, Charles Schneider, Gretchen Genevieve Kimmick, Harold J. Burstein, Larry Norton, Hyman Bernard Muss, Clifford Hudis, Eric P. Winer, Cancer and Leukemia Group B; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Duke Cancer Institute Biostatistics, Durham, NC; University of Chicago, Chicago, IL; Mayo Clinic, Jacksonville, FL; Georgia Cancer Center for Excellence at Grady Memorial Hospital, Atlanta, GA; The Angeles Clinic and Research Institute, Santa Monica, CA; The Ohio State University, Columbus, OH; Southeastern Medical Oncology Center, Goldsboro, NC; Christiana Care Health System, Newark, DE; Duke Cancer Institute, Durham, NC; Memorial Sloan-Kettering Cancer Center, New York, NY; University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC

Background: Determining optimal adjuvant chemotherapy for early stage breast cancer depends on efficacy and toxicity. We sought to determine if T is equivalent to AC but with reduced toxicity. **Methods:** Pts with operable breast cancer with 0-3 positive nodes were enrolled on a 2x2 factorial design study which addressed (1) superiority of 6 vs. 4 cycles of therapy (previously reported, Shulman, *JCO* 2012) and (2) equivalence of single-agent T to standard AC, defined as upper bound of 95% confidence interval (CI) of hazard ratio (HR) of T vs. AC < 1.30 for the primary endpoint of relapse-free survival (RFS). A planned target of 567 RFS events required 4,646 pts with 4 yrs FU. At activation in 2002, T (80mg/m2) was q1wk for 12 or 18 wks and AC (60/600 mg/m2) was q3wk for 4 or 6 cycles. In 2003 (570 pts enrolled) schedules were revised to 4 or 6 cycles q2wk for both T (175 mg/m2) and AC. The 6-cycle arms were dropped in 2008 (3,171 pts enrolled) due to slow accrual. Relative effectiveness of T to AC is shown by hazard ratio (HR). Logrank p-values are measures of discordance but are not relevant for the equivalence question and are not adjusted for multiple comparisons. **Results:** After enrolling 3,871 pts, the study closed in 2010 due to slowing accrual. With a median follow-up of 6.1 yrs there are 437 RFS events. The HR of 1.26 (95% CI: 1.05-1.53; p = 0.02) does not allow a conclusion of equivalence of T with AC. With 266 deaths the HR for overall survival (OS) is 1.27 (95% CI=1.00-1.62; p = 0.05), favoring AC. The estimated absolute advantage of AC at 5 yrs is 3% (91 vs. 88%) for RFS and 1% (95 vs. 94%) for OS. All 9 treatment-related deaths were in pts receiving AC and are included in the survival analysis. The incidence of Grade 3+ toxicity for AC vs T was 33% vs. 4% for hematologic toxicity and 36% vs 22% for non-hematologic toxicity. **Conclusions:** This trial did not show equivalence of T to AC, a conclusion that is very unlikely to change with additional follow-up. T was less toxic than AC. Clinical trial information: NCT00041119.

Abstract: CRA1008

Title: S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer.

Track: Oral Abstract Session, Breast Cancer - Triple-Negative/Cytotoxics/Local Therapy

Authors: G. Thomas Budd, William E. Barlow, Halle C. F. Moore, Timothy J. Hobday, James A. Stewart, Claudine Isaacs, Muhammad Salim, Jonathan K. Cho, Kristine Rinn, Kathy S. Albain, Helen K. Chew, Gary Von Burton, Timothy David Moore, Gordan Srkalovic, Bradley Alexander McGregor, Lawrence E. Flaherty, Robert B. Livingston, Danika Lew, Julie Gralow, Gabriel N. Hortobagyi; Cleveland Clinic, Cleveland, OH; Cancer Research and Biostatistics, Seattle, WA; Mayo Clinic, Rochester, MN; Baystate Medical Center, Springfield, MA; Lombardi Comprehensive Cancer Center, Washington, DC; Allan Blair Cancer Center, Saskatoon, SK, Canada; Oncare Hawaii, Honolulu, HI; Swedish Cancer Institute, Seattle, WA; Loyola University Medical Center, Maywood, IL; University of California, Davis Cancer Center, Sacramento, CA; LSU Health Sciences Center, Shreveport, LA; Mid Ohio Oncology Hematology, Inc., Columbus, OH; Sparrow Regional Cancer Center, Lansing, MI; Willford Hall Medical Center, Lackland, TX; Wayne State University School of Medicine, Detroit, MI; Arizona Cancer Center, Tucson, AZ; Southwest Oncology Group Statistical Center, Seattle, WA; Seattle Cancer Care Alliance, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: S0221 is a SWOG-coordinated phase III adjuvant chemotherapy intergroup trial in node-positive and high-risk node-negative operable breast cancer which hypothesized that 1) the weekly AC+G regimen is superior to ddAC x 6 and 2) 12 weeks of weekly paclitaxel (wP) is superior to q 2 week paclitaxel x 6 (ddP). **Methods:** Between December 2003 and November 2010, 2,716 patients were randomized in a 2 x 2 factorial design to 1) AC+G vs ddAC and 2) P 80 mg/m^2/week x 12 vs P 175 mg/m^2 q 2 weeks x 6. If there was no significant interaction between the factors, the trial was powered to find a disease-free survival hazard ratio (HR) ≤ 0.82 for weekly vs q 2 week for each factor. At the first interim analysis, the AC randomization was halted for futility, and S0221 was closed to accrual 10 November 2010. S0221 reopened 15 December 2010, after which time all patients received 4 cycles of ddAC and randomization to P weekly x 12 and ddP x 6 continued. Accrual halted at a total of 3,294 in January 2012. **Results:** By September 7, 2012, 487 events and 340 deaths had occurred, prompting the third planned interim analysis. The Data Safety and Monitoring Committee recommended reporting the results since the futility boundary was crossed. A Cox model adjusting for the AC arms had a HR = 1.08 (95% CI 0.90-1.28; p=0.42), with the 99.5% CI excluding the original alternative hypothesis that the HR=0.82. There was no significant interaction of the two factors. Estimated 5-year progression-free survivals were 82% for weekly P and 81% for ddP. Toxicity data were available for 1,385 patients treated with ddP and 1,367 treated with weekly P. Grade 5 toxicity occurred in 4 patients on ddP and 2 on weekly P. Percent grade 3-4 toxicity per arm are shown in the Table. **Conclusions:** Either ddPx6 or weekly P x 12 are acceptable schedules of P administration. The differences in leukopenia likely reflect ascertainment bias against weekly P. If this is accepted, weekly P x 12 produces less overall toxicity than 6 cycles of ddP. Support: NCI grants CA32102, CA38926, CA21115, CA21076, CA77597, CA25224, CA77202, CCSRI15469, and Amgen, Inc. Clinical trial information: NCT00070564.

LUNG CANCER

Fadlo Khuri, M.D.

NOTES

Abstract: CRA8007

Title: A randomized study of ganetespib, a heat shock protein 90 inhibitor, in combination with docetaxel versus docetaxel alone for second-line therapy of lung adenocarcinoma (GALAXY-1).

Track: Oral Abstract Session, Lung Cancer - Non-small Cell Metastatic

Authors: Suresh S. Ramalingam, Glenwood D. Goss, Zoran Gojko Andric, Igor Bondarenko, Bojan Zaric, Timur Ceric, Elena Vladimir Poddubskaya, Tudor-Eliade Ciuleanu, James F. Spicer, Enriqueta Felip, Vera Hirsh, Christian Manegold, Rafael Rosell, Fadlo Raja Khuri, Vojislav M. Vukovic, Florentina Teofilovici, Iman El-Hariry, Wei Guo, Safi R. Bahcall, Dean Fennell; The Winship Cancer Institute of Emory University, Atlanta, GA; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; Clinical Hospital Centre Bezanijska Kosa, Beograd, Serbia; Municipal Institution Dnipropetrov, Dnipropetrovsk, Ukraine; University of Novi Sad, Institute for Pulmonary Diseases of Vojvodina, Novi Sad, Serbia; Clinical Center University of Sarajevo, Sarajevo, Bosnia; Unit of Russian Academy of Medical Sciences, Moscow, Russia; Prof. Dr. Ion Chiricuta Institute of Oncology, Department of Medical Oncology, Cluj-Napoca, Romania; King's College London, Guy's Hospital, London, United Kingdom; Thoracic Tumors Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; McGill University Health Centre, Montreal, QC, Canada; University Medical Center, Mannheim, Germany; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Pangaea Biotech, Cancer Therapeutics Innovation Group, USP Institut Universitari Dexeus, Barcelona, Spain; Synta Pharmaceuticals, Inc., Lexington, MA; University of Leicester, Leicester, United Kingdom

Background: Heat shock protein 90 chaperone function is critical for the biological effects of several oncoproteins. Ganetespib (G) is a highly potent 2nd-generation Hsp90 inhibitor with a favorable safety profile and single-agent clinical activity. **Methods:** Based on synergistic preclinical interactions between docetaxel (D) and G, we conducted a randomized (1:1), international open-label study of D with or without G. Patients with advanced lung adenocarcinoma, one prior systemic therapy, and ECOG PS 0/1 were included. D was given at 75 mg/m^2 on day 1 of a three-week cycle. In the experimental arm, D was given on day 1 and G at 150 mg/m^2 on days 1 and 15. The co-primary endpoints were PFS in patients with elevated LDH (eLDH) levels, or tumors harboring KRAS mutations. Key secondary endpoints were OS and PFS in all adenocarcinoma patients. Target enrollment was 240 adenocarcinoma, 120 eLDH, and 80 mKRAS patients. Statistical tests are 1-sided. **Results:** Enrollment of 255 adenocarcinoma patients completed in November 2012; results are reported for this population. Patient characteristics were balanced (median age 60 years, males ~60%, PS 0 ~40% and never-smoker ~25%). For D+G vs. D the median number of cycles delivered was 5 vs. 4; the grade 3/4 adverse events were neutropenia 38% vs. 37%; fatigue 4% vs. 3%; anemia 7% vs. 6%; diarrhea 3% vs. 0; fever with neutropenia 8% vs. 2%. At the time of abstract submission OS HR was 0.69 (90% CI 0.48 to 0.99, p=0.093), the PFS HR was 0.70 (90% CI 0.53 to 0.94, p=0.012), and the ORR was 15% vs 11%, favoring D+G. For patients that were enrolled >6 months after diagnosis of advanced NSCLC (N=175; 69%), a prespecified stratification factor, the OS HR was 0.41 (90% CI 0.25 to 0.67, p=0.0009), the PFS HR was 0.47 (90% CI 0.32 to 0.69, p=0.0005), and the ORR was 16% vs 12%. Updated results for both populations above, as well as for the eLDH and mKRAS subsets, will be presented. **Conclusions:** D+G demonstrated improvement in OS, PFS, and ORR over D alone for second-line therapy of lung adenocarcinoma. A phase III study in second-line advanced adenocarcinoma patients (> 6 months from diagnosis) is ongoing (GALAXY-2). Clinical trial information: NCT01348126.

Abstract: LBA8011

Title: Nintedanib (BIBF 1120) plus docetaxel in NSCLC patients progressing after first-line chemotherapy: LUME Lung 1, a randomized, double-blind phase III trial.

Track: Clinical Science Symposium, Targeted Therapies in Lung Cancer: What's New and What's Enough?

Authors: Martin Reck, Rolf Kaiser, Anders Mellemgaard, Jean Yves Douillard, Sergey Orlov, Maciej Jerzy Krzakowski, Joachim Von Pawel, Maya Gottfried, Igor Bondarenko, Meilin Liao, Jose Barrueco, Birgit Gaschler-Markefski, Silvia Novello; Department of Thoracic Oncology, Grosshansdorf Hospital, Grosshansdorf, Germany; Boehringer Ingelheim GmbH, Biberach, Germany; Department of Oncology, Herlev University Hospital, Herlev, Denmark; Department of Medical Oncology, Centre René Gauducheau, Nantes, France; Department of Thoracic Oncology, St. Petersburg State Medical University, St. Petersburg, Russia; The Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland; Pneumology Clinic, Asklepios Fachkliniken Gauting, Munich, Germany; Lung Cancer Unit, Meir Medical Center, Kfar-Saba, Israel; Municipal Institution Dnipropetrov, Dnipropetrovsk, Ukraine; Shandong Provincial Chest Hospital, Shanghai, China; Boehringer Ingelheim GmbH, Ridgefield, CT; Department of Oncology, University of Turin, Turin, Italy

Background: Nintedanib (N) inhibits VEGFRs, PDGFRs, and FGFRs. LUME Lung 1 is a placebo (P) controlled phase III trial of N + docetaxel (D) in patients (pts) with locally advanced/metastatic NSCLC progressing after first-line therapy. **Methods:** Stage IIIB/IV or recurrent NSCLC pts (stratified by histology, ECOG PS, prior bevacizumab, and brain metastases) were randomized to N 200 mg bid + D 75 mg/m^2 q21d (n=655) or P + D (n=659). 1° endpoint was centrally reviewed PFS after 713 events (2 sided stratified log-rank, α=5%, β=10%). Key 2° endpoint of OS was analyzed hierarchically after 1,121 events (2 sided, adjusted α=4.98%, β=20%), first in adenocarcinoma (adeno) pts <9 mo since start of first-line therapy (T<9mo; identified as a prognostic/predictive biomarker [ASCO '13]), followed by all adeno pts and then all pts. Predefined sensitivity analyses added sum of longest diameters of target lesions (SLD) to stratification factors in the Cox model. Results: Pt characteristics were balanced between the arms. N + D significantly prolonged PFS vs P + D (HR 0.79; CI: 0.68, 0.92; p=0.0019; median 3.4 vs 2.7 mo) regardless of histology (squamous HR 0.77, p=0.02; adeno HR 0.77, p=0.02). OS was significantly prolonged in all adeno pts (HR 0.83; p=0.0359; median 12.6 vs 10.3 mo) with the greatest improvement seen in T<9mo adeno pts (HR 0.75; p=0.0073; median 10.9 vs 7.9 mo). A trend for improved OS was seen in all pts (HR 0.94; p=0.272; median 10.1 vs 9.1). When adjusted for SLD, a significant OS benefit was seen in all pts (HR 0.88; CI: 0.78, 0.99; p=0.0365). Disease control rates were significantly improved with N + D in all adeno pts (odds ratio [OR] 1.93; p<0.0001), T<9mo adeno pts (OR 2.90; p<0.0001) and all pts (OR 1.68; p<0.0001). The most common AEs were diarrhea (any: 42.3 vs 21.8%; Gr ≥3: 6.6 vs 2.6%) and ALT elevations (any: 28.5 vs 8.4%; Gr ≥3: 7.8 vs 0.9%). Incidence of CTCAE Gr ≥3 AEs was 71.3 vs 64.3%. Withdrawals due to AEs (22.7 vs 21.7%) were similar in both arms, as were Gr ≥3 hypertension, bleeding or thrombosis. Conclusions: N + D significantly improved PFS independent of histology, and prolonged OS for adeno pts. AEs were generally manageable with dose reductions and symptomatic treatment. Clinical trial information: NCT00805194.

Abstract: 8008

Title: Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

Track: Oral Abstract Session, Lung Cancer - Non-small Cell Metastatic

Authors: David R. Spigel, Scott N. Gettinger, Leora Horn, Roy S. Herbst, Leena Gandhi, Michael S. Gordon, Cristina Cruz, Paul Conkling, Philippe Alexandre Cassier, Scott J. Antonia, Howard A. Burris, Gregg Daniel Fine, Ahmad Mokatrin, Marcin Kowanetz, Xiaodong Shen, Daniel S. Chen, Jean-Charles Soria; Sarah Cannon Research Institute, Nashville, TN; Yale School of Medicine, New Haven, CT; Vanderbilt University Medical Center, Nashville, TN; Yale University, New Haven, CT; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Pinnacle Oncology Hematology, Scottsdale, AZ; Vall d'Hebron University Hospital, Barcelona, Spain; Virginia Oncology Associates/US Oncology, Norfolk, VA; Centre Léon Bérard, Lyon, France; Moffitt Cancer Center, Tampa, FL; Genentech, Inc., South San Francisco, CA; Genentech Inc., South San Francisco, CA; Institut Gustave Roussy, Villejuif, France

Background: Human lung cancer expresses high levels of PD-L1, which may inhibit anti-cancer immune responses. MPDL3280A, a human monoclonal Ab containing an engineered Fc-domain designed to optimize efficacy and safety, targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. **Methods:** Pts with squamous or nonsquamous NSCLC received MPDL3280A IV q3w at doses between 1-20 mg/kg in a Ph I expansion study. Pts were treated for up to 1 y. Objective response rate (ORR) was assessed by RECIST v1.1. Reported ORR includes u/cCR and u/cPR. **Results:** As of Jan 10, 2013, 53 NSCLC pts were evaluable for safety and treated at doses of ≤1 (n=2), 10 (n=10), 15 (n=19) and 20 mg/kg (n=22). Pts had a median age of 61 y (range 24-83 y), 98% were PS 0-1, 89% had prior surgery and 55% had prior radiotherapy. 98% of pts received prior systemic therapy. Pts received treatment for a median duration of 106 days (range 1-324) of MPDL3280A. The incidence of all G3/4 AEs, regardless of attribution, was 34%, including pericardial effusion (6%), dehydration (4%), dyspnea (4%) and fatigue (4%). No G3-5 pneumonitis or diarrhea was reported. 37 NSCLC pts enrolled prior to Jul 1, 2012, were evaluable for efficacy. RECIST responses were observed at dose levels between 1 and 20 mg/kg, with all responses ongoing or improving. An ORR of 24% (9/37) was observed in pts with squamous and nonsquamous histologies, including several with rapid tumor shrinkage. Additional pts had delayed responses after apparent radiographic progression (not included in the ORR). The 24-week PFS was 48%. Analysis of biomarker data from archival tumor samples demonstrated a correlation between PD-L1 status and efficacy. Pts who were PD-L1 tumor status–positive showed an ORR of 100% (4/4) and a PD rate of 0% (0/4), while pts who were PD-L1 tumor status–negative showed an ORR of 15% (4/26) and a PD rate of 58% (15/26). Updated data will be presented. **Conclusions:** Treatment with MPDL3280A was well tolerated, with no pneumonitis-related deaths. Rapid and durable responses were observed. PD-L1 tumor status correlated with response to MPDL3280A. Clinical trial information: NCT01375842.

Abstract: LBA8003

Title: Randomized, open-label, phase III study of pemetrexed plus carboplatin (PemC) followed by maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab (PCB) followed by maintenance bevacizumab in patients with advanced nonsquamous (NS) non-small cell lung cancer (NSCLC).

Track: Lung Cancer - Non-small Cell Metastatic

Authors: Ralph Zinner, Helen J. Ross, Robert Weaver, Ramaswamy Govindan, Viran R. Holden, Naveed Mahfooz Chowhan, J. Thaddeus Beck, David Michael Waterhouse, Manuel Modiano, Vijay Phooshkooru Rao, Jingyi Liu, Andrew Koustenis, Symantha Melemed, Susan C. Guba, Waldo Feliu Ortuzar, Durisala Desaiah, David R. Spigel, Coleman K. Obasaju; The University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic, Scottsdale, AZ; Florida Cancer Specialists, Tampa, FL; Washington University School of Medicine in St. Louis, St. Louis, MO; St Johns Clinic, Springfield, MO; Cancer Care Center Inc., New Albany, IN; Highlands Oncology Group, Fayetteville, AR; Oncology Hematology Care/SCRI, Cincinnati, OH; Arizona Clinical Research Center and Arizona Oncology, Tucson, AZ; Mid Dakota Clinic, Bismarck, ND; Eli Lilly and Company, Indianapolis, IN; Sarah Cannon Research Institute, Nashville, TN

Background: Ralph Zinner, Helen J. Ross, Robert Weaver, Ramaswamy Govindan, Viran R. Holden, Naveed Mahfooz Chowhan, J. Thaddeus Beck, David Michael Waterhouse, Manuel Modiano, Vijay Phooshkooru Rao, Jingyi Liu, Andrew Koustenis, Symantha Melemed, Susan C. Guba, Waldo Feliu Ortuzar, Durisala Desaiah, David R. Spigel, Coleman K. Obasaju; The University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic, Scottsdale, AZ; Florida Cancer Specialists, Tampa, FL; Washington University School of Medicine in St. Louis, St. Louis, MO; St Johns Clinic, Springfield, MO; Cancer Care Center Inc., New Albany, IN; Highlands Oncology Group, Fayetteville, AR; Oncology Hematology Care/SCRI, Cincinnati, OH; Arizona Clinical Research Center and Arizona Oncology, Tucson, AZ; Mid Dakota Clinic, Bismarck, ND; Eli Lilly and Company, Indianapolis, IN; Sarah Cannon Research Institute, Nashville, TN

Abstract: 7503

Title: Neoadjuvant chemotherapy with or without preoperative irradiation in stage IIIA/N2 non-small cell lung cancer (NSCLC): A randomized phase III trial by the Swiss Group for Clinical Cancer Research (SAKK trial 16/00).

Track: Oral Abstract Session, Lung Cancer - Non-small Cell Local-regional/Small Cell/Other Thoracic Cancers

Authors: Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A. Stahel, Walter Weder, Sandra Thierstein, Alexandros Xyrafas, Martin Frueh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R. Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C. Betticher, Rene-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group; Medical Oncology and Tumorcenter Kantonsspital Winterthur, Winterthur, Switzerland; University of Lausanne Hospitals (CHUV), Lausanne, Switzerland; Department of Surgery, Center Hospitalier Universitaire de Vaud, Lausanne, Switzerland; University Hospital Zurich, Zurich, Switzerland; Department of Thoracic Surgery, University Hospital, Zürich, Switzerland; SAKK - Swiss Group for Clinical Cancer Research, Coordinating Center, Berne, Switzerland; Medical Oncology, Kantonsspital St. Gallen, St. Gallen, Switzerland; Department of Medical Oncology, Kantonsspital Graubuenden, Chur, Switzerland; University Hospital Basel, Basel, Switzerland; University Hospital Geneva, Geneva, Switzerland; Department of Thoracic Surgery, Hospital of Pulmonary diseases, NoviSad, Serbia; Department of Medical Oncology, University Hospital, Bern, Switzerland; Department of Radio-Oncology, Kantonsspital, Winterthur, Switzerland; Department of Medical Oncology, Kantonsspital, Aarau, Switzerland; Regionalspital Thun, Thun, Switzerland; Medical Oncology, Kantonsspital Luzern, Lucerne, Switzerland; Hospital of Fribourg, Fribourg, Switzerland; Centre Hospitalier Univ Vaudois, Lausanne, Switzerland; Centre Hospitalier Universitaire de Vaud, Lausanne, Switzerland

Background: For stage III/N2 NSCLC neoadjuvant chemotherapy (NCT) followed by radical surgery is one standard treatment approach. In our previous trial, this strategy led to a median survival of 33 months (Betticher et al. JCO 2003). We now investigated whether the addition of preoperative radiotherapy (RT) would improve outcome. We report the results of a planned interim analysis on data of the first 219 patients (pts). The trial was closed to accrual in December 2012 due to futility after enrollment of 232 of 240 planned pts. **Methods:** Pts with pathologically proven, resectable stage IIIA/N2 NSCLC, performance status 0-1, adequate heart, kidney, liver and bone marrow function were randomized 1:1 to receive 3 cycles of NCT (cisplatin 100 mg/m2 and docetaxel 85 mg/m2 d1, q3weeks) followed by accelerated concomitant boost RT (44 Gy/22 fractions in 3 weeks) or NCT alone, with subsequent surgery for all pts. The primary endpoint was event-free survival (EFS). **Results:** 23 centers included 219 pts. Median age was 60 years. Pts characteristics were well balanced. Toxicity to CT was substantial, but 91% completed 3 cycles of NCT. RT-induced grade 3 esophagitis was seen in 5 pts, grade 3 skin toxicity in 2 pts. One pt in each treatment arm died during NCT, there was one postoperative death (arm NCT alone). The efficacy results are summarized below, all comparisons are statistically non-significant. **Conclusions:** This is the first completed phase III trial to investigate the value of the addition of neoadjuvant radiotherapy to CT and surgery. RT did not improve EFS or survival, nor did it reduce the local failure rate. Nevertheless, the overall survival rates of our neoadjuvant chemotherapy strategy confirm our previous report, and are among the best results reported to date in a multicenter setting. Clinical trial information: NCT00030771.

Abstract: 7501

Title: A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617.

Track: Lung Cancer - Non-small Cell Local-regional/Small Cell/Other Thoracic Cancers

Authors: Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory A. Masters, Kenneth Forster, Steven E. Schild, Jeffrey Bogart, Yolanda I. Garces, Samir Narayan, Vivek Kavadi, Lucien Alexander Nedzi, Jeff M. Michalski, Douglas Johnson, Robert Malcolm MacRae, Walter John Curran, Hak Choy, Radiation Therapy Oncology Group; Washington University School of Medicine in St. Louis, St. Louis, MO; Radiation Therapy Oncology Group, Statistical Center, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; Helen F. Graham Cancer Center, Christiana Care, Newark, DE; Moffitt Cancer Center, Tampa, FL; Mayo Clinic, Scottsdale, AZ; SUNY Upstate Medical University, Syracuse, NY; Mayo Clinic, Rochester, MN; St Joseph Mercy Hosp, Ann Arbor, MI; Texas Oncology, Sugarland, TX; The University of Texas Southwestern Medical Center, Dallas, TX; Florida Radiation Oncology Group, Jacksonville, FL; The Ottawa Hospital, Ottawa, ON, Canada; Emory University, Atlanta, GA

Background: The first objective of RTOG 0617 was to compare the overall survival(OS) of patients(pts) treated with standard-dose(SD)(60Gy) versus high-dose(HD)(74Gy) radiotherapy with concurrent chemotherapy(CT). **Methods:** This Phase III Intergroup trial randomized 464 pts with Stage III NSCLC to the SD(60Gy) vs. HD(74Gy) arms prior to closure of the HD arm. Concurrent CT included weekly paclitaxel(45 mg/m2) and carboplatin(AUC=2). Pts randomized to cetuximab received a 400 mg/m2 loading dose on Day 1 followed by weekly doses of 250 mg/m2. All pts were to receive consolidation CT. We are reporting the final results on radiation dose. **Results:** 464 pts were accrued prior to closure of the HD arm in 6/11, of which 419 were eligible for analysis. Median follow up was 17.2 months. There were 2 and 10 grade 5 treatment-related adverse events(AEs) on the SD and HD arms, respectively. Grade 3+AEs were 74.2% and 78.2% on SD and HD arms, respectively (p=0.34). The median survival times and 18-month OS rates for the SD and HD arms were 28.7 vs 19.5 months, and 66.9% vs 53.9% respectively (p=0.0007). The primary cause of death was lung cancer (72.2% vs 73.5%)(p=0.84). Local failure rates at 18 months were 25.1% vs 34.3% for SD and HD patients, respectively(p=0.03). Local-regional and distant failures at 18 months were 35.3% vs 44%(p=0.04) and 42.4% vs 47.8%(p=0.16) for SD and HD arms, respectively. Factors predictive of less favorable OS on multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume >5 Gy. **Conclusions:** In this setting of chemoradiation for locally-advanced Stage III NSCLC, 60 Gy is superior to 74 Gy in terms of OS and local-regional control. The effect of the anti-EGFR antibody (cetuximab) awaits further follow up. This project was supported by RTOG grant U10 CA21661, CCOP grant U10 CA37422, and ATC U24 CA 81647 from the National Cancer Institute (NCI) and Eli Lilly and Company. Clinical trial information: NCT00533949.

HEAD AND NECK CANCER

Fadlo Khuri, M.D.

NOTES

Abstract: 6009

Title: The Cancer Genome Atlas: Integrated analysis of genome alterations in squamous cell carcinoma of the head and neck**.**

Track: Clinical Science Symposium, Does the Genetic Landscape Drive Therapeutic Targeting in Head and Neck Cancer?

Authors: David N. Hayes, Jennifer R. Grandis, Adel K. El-Naggar; Lineberger Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Pittsburgh, Pittsburgh, PA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Head and neck squamous cell carcinoma (HNSCC) is a leading cause of cancer death in worldwide. **Methods:** The Cancer Genome Atlas (TCGA) is conducting DNA, RNA and miRNA sequencing along with DNA copy number profiling, quantification of mRNA expression, promoter methylation, and reverse-phase protein arrays on surgically resected samples from previously untreated patients with HNSCC. We report for the first time the integrated genomic alterations for 279 HNSCC patients. **Results:** The demographics of 279 patients enrolled in the study show a median age of 61 years (range: 19-90); 27% female, and history of tobacco smoking in 80%. Over 30 sites of significant somatic copy number alteration were identified as well as 15 significantly mutated genes at the false fiscovery rate of <0.01, including: CDKN2A, TP53, PIK3CA, FAT1, MLL2, TGFBR2, HLA-A, NOTCH1, HRAS, NFE2L2, and CASP8. Evidence of the human papilloma virus (HPV) was observed by sequencing in up to 25% of samples. Integrated genomics data supported expected patterns including the predominant role of HPV type 16 infection in nonsmoking patients with tumors of the oropharynx which are wild-type for the tumor suppressor genes p16, Rb, and p53. In addition, striking atypical cases and viral infections will be presented as well as novel anti-correlation of HPV infection with focal copy number alterations including EGFR amplification and chromosome 11q. By contrast co-occurrence of HPV with focal deletions of TRAF3 and mutations of the oncogene PIK3CA will be described. Integrated tumor subtypes defined by gene expression, methylation, and miRNA will be presented in conjunction with associated mutations exclusive to tumor subtypes. For example, alterations of the “antioxidant response elements” transcription activators NFE2L2 and KEAP1 will be documented in association with the “classical” expression subtype of HNSCC, as has been shown in lung squamous cell carcinoma. By contrast, co-occurrence of CASP8 and HRAS will be documented in the “Basal” subtype. **Conclusions:** While, HNSCC is a heterogeneous tumor, coordinated tumor alterations are observed, including potentially targetable genes and pathways. Results presented on behalf of TCGA.

GYNECOLOGIC CANCER

Sharad Ghamande, M.D.

NOTES

Abstract: 3

Title: Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: A phase III randomized trial of the Gynecologic Oncology Group.

Track: Plenary Session, Plenary Session Including FDA Commissioner Address, Public Service Award, and Science of Oncology Award and Lecture

Authors: Krishnansu Sujata Tewari, Michael Sill, Harry J. Long, Lois M. Ramondetta, Lisa Michelle Landrum, Ana Oaknin, Thomas J Reid, Mario M. Leitao, Helen E Michael, Bradley J. Monk; University of California, Irvine, Medical Center, Orange, CA; Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY; Mayo Clinic, Rochester, MN; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Vall d'Hebron University Hospital, Barcelona, Spain; University of Cincinnati, Cincinnati, OH; Memorial Sloan-Kettering Cancer Center, New York, NY; Clarian North Medical Center, Carmel, IN; Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ

Background: Vascular endothelial growth factor (VEGF) promotes angiogenesis, a mediator of disease progression in cervical cancer. Bevacizumab (B), a humanized anti-VEGF monoclonal antibody, has shown single-agent activity in pretreated recurrent disease. We aimed to evaluate B in chemotherapy (CTX)-naive recurrent/persistent/metastatic cervical cancer. **Methods:** Using a 2x2 factorial design, patients were randomly assigned to CTX with or without B 15 mg/kg. The CTX regimens included cisplatin 50 mg/m^2 plus paclitaxel 135-175 mg/m^2 and topotecan 0.75 mg/m^2 d1-3 plus paclitaxel 175 mg/m^{2}d1. Cycles were repeated every 21 days until disease progression, unacceptable toxicity, or complete response. Overall survival (OS) was the primary endpoint with a reduction in the hazard of death by 30% using anti-VEGF therapy considered important (90% power, 1-sided alpha=2.5%). Final analysis was planned when 346 deaths were observed. **Results:** 452 patients were accrued from 4/6/09 to 1/3/12. The scheduled interim analysis occurred after 174 patients had died and showed that the topotecan-paclitaxel backbone was not superior to the cisplatin-paclitaxel backbone. A second interim analysis was conducted after 271 deaths. A total of 225 patients received CTX alone and 227 patients received CTX plus B. The randomized treatment groups were similar with regard to age, histology, performance status, previous platinum as a radiosensitizer, and recurrence, persistence, or advanced disease. The B-to-no-B hazard ratio (HR) of death was 0.71 (97.6% CI 0.54-0.95; 1-sided p=0.0035). Median survival was 17 m (CTX plus B) and 13.3 m (CTX alone). The RR were 48% (CTX plus B) and 36% (CTX alone) (p=0.0078). Treatment with B was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%). **Conclusions:** For the first time a targeted agent significantly improved OS in gynecologic cancer. The second interim analysis crossed the boundary for efficacy, warranting early release of this information. The nearly 4-month increase in median OS with the addition of B to CTX in women with recurrent cervical cancer is considered to be clinically significant. Clinical trial information: NCT00803062.

Abstract: LBA5501

Title: A randomized multicenter phase III study comparing weekly versus every 3 weeks carboplatin (C) plus paclitaxel (P) in patients with advanced ovarian cancer (AOC): Multicenter Italian Trials in Ovarian Cancer (MITO-7)—European Network of Gynaecological Oncological Trial Groups (ENGOT-ov-10) and Gynecologic Cancer Intergroup (GCIG) trial.

Track: Oral Abstract Session, Gynecologic Cancer

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Background: Three-weekly (3w) CP is standard first-line chemotherapy for AOC pts. Weekly (w) P combined with 3w C prolonged PFS and OS in a JGOG phase III trial. MITO-7 is an academic randomized phase III study, comparing 3w vs. w CP. **Methods:** AOC chemonaive pts, stage IC-IV, age≤75, ECOG PS≤2, were randomized to 3wCP (C AUC6 + P 175mg/m², d1q21) for 6 cycles or to wCP (C AUC2 + P 60mg/m²) for 18 administrations. Coprimary endpoints were PFS and quality of life (QoL), measured by FACT-O and FACT/GOG-Ntx. With 80% power in detecting HR of 0.75, 2-sided α=0.05, 383 events were needed for PFS analysis. The arms were compared with a log-rank test and in a Cox model adjusted by stage, PS, residual disease, age and size of institution, following intention-to-treat. QoL was measured at baseline and weekly for 9 wks. Interaction between arm and QoL time was tested in a linear mixed model. Toxicity was coded by NCI-CTCAE v3.0. **Results:** 822 pts were enrolled by MITO, MANGO, and GINECO. Median age was 60; stage III (66%) and IV (18%) were prevalent. As of March 18, 2013, with median follow-up 20 months, 410 PFS events were recorded. Median PFS was 18.8 months with wCP and 16.5 months with 3wCP (HR 0.88, 95%CI 0.72-1.06, p=0.18). Lack of significant difference was confirmed (HR 0.87, 95%CI 0.71-1.05) in Cox model. For all scores, QoL course was significantly different between arms (p<0.0001). With 3wCP, QoL scores clearly worsened after each chemotherapy course (weeks 1, 4, 7), whilst with wCP, after a small and transient worsening at week 1, scores remained stable. Considering severe grades (≥3), wCP produced significantly less neutropenia, febrile neutropenia, thrombocytopenia, renal toxicity, and neuropathy. **Conclusions:** Compared to standard CP every 3 weeks, weekly CP did not demonstrate a significant benefit in PFS, but was associated with better QoL and toxicity. Clinical trial information: NCT00660842.

Abstract: LBA5503

Title: Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC): Results of an international Intergroup trial (AGO-OVAR16)

Track: Oral Abstract Session, Gynecologic Cancer

Authors: Andreas Du Bois, Anne Floquet, Jae Weon Kim, Jörn Rau, Jose Maria Del Campo, Michael Friedlander, Sandro Pignata, Keiichi Fujiwara, Ignace Vergote, Nicoletta Colombo, Mansoor Raza Mirza, Bradley J. Monk, Pauline Wimberger, Isabelle Ray-Coquard, Rongyu Zang, Ivan Diaz-Padilla, Klaus H. Baumann, Jae Hoon Kim, Philipp Harter, on behalf of an Intergroup consortium; Kliniken Essen Mitte, Essen, Germany; Institut Bergonié, Bordeaux, France; Seoul National University College of Medicine, Seoul, South Korea; Philipps University Marburg, Marburg, Germany; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Prince of Wales Hospital, Sydney, Australia; National Cancer Institute of Naples, Naples, Italy; Saitama Medical University International Medical Center, Saitama, Japan; UZ Leuven, Leuven, Belgium; University of Milan-Bicocca, Milan, Italy; Department of Oncology; Rigshospitalet; Copenhagen University Hospital, Copenhagen, Denmark; Creighton University School of Medicine at St. Joseph's Hospital and Medical Center, Phoenix, AZ; Department of Gynecology and Obstetrics, University of Duisburg-Essen, Essen, Germany; Centre Léon Bérard, Lyon, France; Shanghai Fudan University, Shanghai, China; Department of Medical Oncology, Centro Integral Oncologico "Clara Campal", Madrid, Spain; Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: Pazopanib is an oral, multikinase inhibitor of VEGFR-1, -2, -3, PDGFR-α and -β, and c-Kit. Preclinical and clinical studies support VEGF(R) and PDGF(R) as targets for AEOC treatment. This study evaluated the efficacy, safety, and tolerability of pazopanib maintenance therapy in patients who have not progressed after first-line chemotherapy for AEOC. **Methods:** Patients with histologically confirmed AEOC, FIGO II-IV, and no evidence of progression after surgery and ≥ 5 cycles of platinum-taxane chemotherapy were randomized 1:1 to receive 800 mg pazopanib once daily or placebo for up to 24 months. Primary endpoint was progression-free survival (PFS) by RECIST. Secondary endpoints included overall survival, PFS by GCIG criteria, safety, and quality of life. **Results:** Most of the 940 randomized patients had stage III/IV disease (91%) at initial diagnosis, and no residual disease after surgery (58%). The median time from diagnosis to randomization was 7.1 months in the placebo arm and 7.0 months in the pazopanib arm. The median follow-up was 24 months. Patients in the pazopanib arm had a prolonged PFS vs placebo (HR = 0.766; 95% CI: 0.64-0.91; p = 0.0021; medians 17.9 vs 12.3 months, respectively). Sensitivity and subgroup analyses of PFS, and analysis of PFS by GCIG criteria, were consistent with the primary analysis. The first interim analysis for OS (only 189 OS events = 20.1% of population) showed no difference between arms. Pazopanib mean exposure was shorter vs placebo (8.9 vs 11.7 months). Pazopanib treatment was associated with a higher incidence of adverse events (AEs) and serious AEs (26% vs 11%) vs placebo. The most common AEs were hypertension, diarrhea, nausea, headache, fatigue, and neutropenia. Fatal SAEs were reported in three patients on pazopanib and one patient on placebo. **Conclusions:** Pazopanib maintenance therapy provided a statistically significant and clinically meaningful PFS benefit in patients with AEOC; OS data are not mature. The safety profile of pazopanib in this setting was consistent with its established profile. Clinical trial information: NCT00866697.

GASTROINTESTINAL CANCER

Bassel El-Rayes, M.D.

NOTES

Abstract: 3505

Title: FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group.
Track: Oral Abstract Session, Gastrointestinal (Colorectal) Cancer

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Background: Doublets plus bev are a standard option for the first-line treatment of mCRC. First-line FOLFOXIRI demonstrated superior RR, PFS and OS compared to FOLFIRI. A phase II study of FOLFOXIRI/bev showed promising activity and manageable toxicities. The objective of the TRIBE trial was to confirm the superiority of FOLFOXIRI vs FOLFIRI when bev is added to chemotherapy (CT). **Methods:** Eligibility criteria included: measurable and unresectable mCRC, age 18-75 years, no prior CT for advanced disease. Pts were randomized to either FOLFIRI/bev (arm A) or FOLFOXIRI/bev (arm B). Both treatments were administered for a maximum of 12 cycles followed by 5FU/bev until progression. Primary endpoint was PFS. **Results:** Between July 2008 and May 2011 508 pts were randomized. Pts characteristics were (arm A/arm B): median age 60/61, ECOG PS 1-2 11%/10%, synchronous metastases 81%/79%, multiple sites of disease 74%/70%, liver-only disease 18%/23%, prior adjuvant (adj) 12%/12%. At a median follow-up of 26.6 mos 424 pts progressed and 244 died. Median PFS and OS in the intention to treat (ITT) population were 10.9 and 30.9 mos. FOLFOXIRI/bev significantly increased PFS (median 9.7 vs 12.2 mos, HR 0.73 [0.60-0.88] p=0.0012). Subgroup analyses based on stratification factors (PS, prior adj) and baseline characteristics (site of primary, liver only disease, resection of primary, Kohne score) did not evidence significant interactions between treatment and analyzed factors. A trend toward a more consistent effect of FOLFOXIRI/bev was reported in no prior adj (HR 0.68 [0.55-0.83]) compared to prior adj group (HR 1.18 [0.67-2.08], p for interaction=0.071). Response rate (RECIST) was also significantly improved (53% vs 65% p=0.006). FOLFOXIRI/bev did not increase the R0 secondary resection rate in the ITT population (12% vs 15%, p=0.327), or in the liver-only subgroup (28% vs 32%, p=0.823). **Conclusions:** FOLFOXIRI/bev compared to FOLFIRI/bev, significantly increases PFS and response rate. Subgroup analysis suggests a possible interaction between prior adj CT and PFS benefit. Secondary resection rate does not differ between treatment arms. Clinical trial information: NCT00719797.

Abstract: 3502

Title: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG)

Track: Gastrointestinal (Colorectal) Cancer

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Background: The optimal duration of chemotherapy and bevacizumab in mCRC is not well established. The CAIRO3 study investigated the efficacy of maintenance treatment with capecitabine plus bevacizumab versus observation in mCRC pts not progressing during induction treatment with capecitabine, oxaliplatin and bevacizumab (CAPOX-B). **Methods:** Previously untreated mCRC pts, PS 0-1, with stable disease or better after 6 cycles of CAPOX-B, not eligible for metastasectomy and eligible for future treatment with oxaliplatin, were randomized between observation (arm A) or maintenance treatment with capecitabine 625 mg/m2 bid dailycontinuouslyand bevacizumab 7.5 mg/kg iv q 3 weeks (arm B). Upon first progression (PFS1), pts in both arms were treated with CAPOX-B until second progression (PFS2, primary endpoint). For pts not able to receive CAPOX-B upon PFS1, PFS2 was considered equal to PFS1. Secondary endpoints were overall survival (OS) and time to second progression (TTP2), which was defined as the time to progression or death on any treatment following PFS1. All endpoints were calculated from the time of randomization. **Results:** A total of 558 pts were randomized. Median follow-up is 33 months. The median number of maintenance cycles in arm B was 9 (range 1-54). The median PFS1 in arm A vs B was 4.1 vs 7.4 months (HR 0.44, 95% CI 0.37-0.54, p<0.0001). Upon PFS1, 72% of pts received CAPOX-B in arm A and 44% in arm B. The median PFS2 was 10.4 vs 10.4 months (HR 0.86, 95% CI 0.7-1.04, p=0.12). The median TTP2 in arm A vs B was 11.5 vs 15.4 months (HR 0.58, 95% CI 0.48-0.72, p<0.0001), and the median OS was 17.9 vs 21.7 months (HR 0.77, 95% CI 0.62-0.96, p=0.02), respectively. **Conclusions:** Maintenance treatment with capecitabine plus bevacizumab after 6 cycles CAPOX-B did not significantly prolong PFS2, which may be due to the lower number of pts in arm B that received CAPOX-B following PFS1. Maintenance treatment significantly prolonged PFS1, TTP2 and OS. Our data support the use of bevacizumab plus capecitabine until progression or unacceptable toxicity. Updated results will be presented. Clinical trial information: NCT00442637.

Abstract: 3504

Title: A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study.
Track: Oral Abstract Session, Gastrointestinal (Colorectal) Cancer

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Background: Resection of liver metastases from colorectal cancer with or without neoadjuvant chemotherapy is the standard of care. The EPOC study (Nordlinger et al, Lancet 2008) randomised patients between surgery and surgery with chemotherapy and demonstrated an improvement in 3 year progression free survival (PFS) of 7·3% (from 28·1% to 35·4%). As a rational extension to the EPOC study data, the New EPOC study evaluates the benefit of cetuximab, an EGF receptor antibody, in addition to standard chemotherapy in patients with operable liver metastases. **Methods:** 272 patients were randomised between February 2007 and November 2012 into the New EPOC study. Eligible patients were required to be k-RAS wild type, have operable liver metastases and to be sufficiently fit for chemotherapy and surgery. Patients with the primary tumour in situ, and those who required short course rectal radiation were eligible. Patients were randomised to receive a fluoropyrimidine and oxaliplatin plus or minus cetuximab for 12 weeks before, then 12 weeks following surgery. Patients who had been treated with adjuvant oxaliplatin could receive irinotecan and 5 – fluorouracil. **Results:** Following a recommendation from the Independent Data Monitoring Committee on 19/11/2012, the New EPOC study was stopped when the study met a protocol pre-defined futility analysis. With 45.3% (96/212) of the expected events observed, progression free survival was significantly worse in the cetuximab arm (14.8 vs 24.2 months, HR (95%CI) 1.50037 (1.000707 to 2.249517) p< 0.048). The result of a pre-planned analysis excluding the 23 patients treated with irinotecan based chemotherapy was similar (15.2 vs 24.2 months, HR 1.565546 (1.014967-2.414793) P<0.043). **Conclusions:** Although the data are immature, the accumulation of more events is unlikely to change this result. In patients with resectable liver metastases and K-RAS wt tumours the addition of cetuximab to chemotherapy is not beneficial. Clinical trial information: ISRCTN22944367.

Abstract: LBA4003

Title: Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study.

Track: Oral Abstract Session, Gastrointestinal (Noncolorectal) Cancer

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Background: CRT in patients with LAPC controlled after induction CT could be superior to continuing CT (Huguet, JCO 2007). The role of erlotinib is unknown. We aimed to define the role of 1) CRT after disease control with gemcitabine, 2) erlotinib in LAPC. **Methods:** LAPC PS 0-2 patients were first randomized to gemcitabine alone or plus erlotinib 100 mg/d for 4 months (R1, stratification: center, PS). Patients with controlled disease were then randomized to 2 additional months of CT (Arm 1) or CRT (Arm 2) 54 Gy and capecitabine 1600 mg/m^2/d (R2, stratification: center, initial arm). Patients receiving erlotinib at R1 had maintenance with this drug after protocol completion. Quality control for radiotherapy included dummy runs and assessment of treated patients. Primary objective: overall survival (OS) in R2 patients. Secondary objectives: role of erlotinib on OS (R1), tolerance, predictive markers, and circulating tumor cells. Taking into account a 30% progression rate between R1 and R2, and 5% lost to follow-up, 722 patients were required to observe 392 deaths to show a median OS increase from 9 to 12 m (HR=0.75) in the CRT arm (2 sided α=5% and β=20%) with planned interim analyses using alpha spending function and O'Brien Fleming boundaries (to reject H0 or H1). Kaplan-Meier, log rank and univariate Cox tests were used. **Results:** From 442 pts included for R1, 269 pts reached R2 (arm1:136; arm 2:133). Main baseline characteristics in arms 1/2: female 44%/56%, mean age 63/62, head tumor 65%/62%, PS 0 56%/48%. After a median follow-up of 36 m, 221 deaths had occurred allowing the planned interim analysis (information fraction 56.4%). OS in R2 pts was 16.5 m [15.5-18.5] and 15.3 m [13.9–17.3] in arms 1 and 2, respectively (HR=1.03 [0.79-1.34], p=0.83). IDMC has confirmed that the futility boundary for the hypothesis of CRT superiority was crossed and considered this as the final analysis of the study. **Conclusions:** Administering CRT is not superior to continuing CT in patients with controlled LAPC after 4 months of CT. Clinical trial information: NCT00634725.

Abstract: 4023

Title: Cougar-02: A randomized phase III study of docetaxel versus active symptom control in patients with relapsed esophago-gastric adenocarcinoma.

Track: Oral Abstract Session, Gastrointestinal (Noncolorectal) Cancer

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Background: Survival in patients who relapse after first-line chemotherapy (CT) for advanced esophago-gastric adenocarcinoma (EGC) is poor though recently randomised trials (RCT) have suggested a small benefit for second line chemotherapy with taxanes or irinotecan. There is very little data on health related quality of life (HRQL) or overall survival (OS), particularly in patients who progress shortly after first-line therapy. **Methods:** COUGAR-02 was a multicentre open-label, phase III RCT for patients with locally advanced or metastatic EGC of performance status (PS) 0-2 who had progressed within 6 months of previous platinum/fluoropyrimidine CT. Patients were randomised (1:1) to receive either docetaxel 75mg/m^2every 3 weeks for up to 6 cycles or active symptom control (ASC). The primary endpoint was OS. The secondary endpoint of HRQL, assessed using EORTC QLQ-C30 and QLQ-ST022, was analysed using standardised area under a curve and compared using Wilcoxon rank sum test. Sensitivity analysis adjusting for dropouts due to death were performed using quality adjusted survival. **Results:** 168 patients **(**84 patients in each arm) were recruited between April 2008 and April 2012. Median age was 65 years (range 28-84); 81% were males. PS at randomisation was 0 for 27%, 1 for 57% and 2 for 15%. 86% had metastatic disease. 43% progressed during previous CT, 28% progressed within 3 months of end of previous CT and 29% progressed between 3 and 6 months. Median number of cycles of docetaxel was 3. 23% completed 6 cycles. Docetaxel was well tolerated and resulted in a significantly improved OS over ASC alone (HR=0.67 (95% CI 0.49-0.92); p=0.01). Objective response rate was 7%. For QLQ-C30, patients on docetaxel arm reported significantly less pain (p=0.0008) and trend for less nausea and vomiting (p=0.02) and constipation (p=0.02) than those on ASC arm. Similar global HRQL seen (p=0.53).For QLQ-ST022, trend seen for less dysphagia (p=0.02) and pain symptoms (p=0.01) for patients on docetaxel arm than ASC **Conclusions:** Docetaxel provided a significant OS benefit over ASC with improvements in symptom scores and no loss in overall HRQL. Docetaxel can be considered a standard of care in this setting. Clinical trial information: NCT00978549.

Abstract: LBA3506

Title: Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3).

Track: Oral Abstract Session, Gastrointestinal (Colorectal) Cancer

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Background: In patients (pts) with KRAS, wild-type metastatic colorectal cancer (mCRC) a head to head comparison of anti-EGFR- and anti-VEGF-directed first-line therapy has not been reported with regard to the FOLFIRI backbone. The AIO KRK-0306 study was therefore designed as a randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in mCRC pts not pretreated for metastatic disease. **Methods:** Pts were randomized to FOLFIRI (Tournigand regimen) every two wks plus cetuximab (400 mg/m² day 1, followed by 250 mg/m² wkly = arm A) or bevacizumab (5 mg/kg every two wks = arm B). The intent-to-treat (ITT) population comprised all pts who had at least completed one application of therapy. While recruitment initially was independent of KRAS status, an amendment confined inclusion to KRAS wildtype (WT) tumors. Recruitment was completed in October 2012. The primary study endpoint was objective response rate (ORR, investigators read). **Results:** Among 735 pts of the ITT-population, KRAS-WT was identified in 592. Of these, 297 pts were randomized to arm A and 295 to arm B. Median age was 64 years, 66% of pts were male, and ECOG PS 0-1 was observed in 98% of pts. Median duration of treatment was 4.7 mo vs 5.3 mo, respectively. While in the ITT analysis, ORR was comparable in arms A vs B (62% vs 57%, odds ratio 1.249), a significant superiority was found for assessable pts in arm A. Median PFS of the ITT population was nearly identical (10.3 vs 10.4 mo, HR 1.04, p=0.69), however, overall survival (OS) showed a significantly better outcome in arm A vs arm B (28.8 vs 25.0 mo, HR 0.77, p=0.0164, 95% CI: 0.620-0.953). Sixty-day mortality was low in both arms (1.01% vs 2.71%). **Conclusions:** ORR was comparable between arms in the ITT analysis, but favored arm A in assessable pts. Significantly superior OS was observed in KRAS-WT patients receiving cetuximab plus FOLFIRI as first-line treatment. Clinical trial information: NCT00433927.

Abstract: 4005

Title: Results of a randomized phase III trial (MPACT) of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates.
Track: Oral Abstract Session, Gastrointestinal (Noncolorectal) Cancer

Authors: Daniel D. Von Hoff, Thomas J. Ervin, Francis P. Arena, E. Gabriela Chiorean, Jeffrey R. Infante, Malcolm J. Moore, Thomas E. Seay, Sergei Tjulandin, Wen Wee Ma, Mansoor N. Saleh, Marion Harris, Michele Reni, Ramesh K. Ramanathan, Josep Tabernero, Manuel Hidalgo, Eric Van Cutsem, David Goldstein, Xinyu Wei, Jose Luis Iglesias, Markus Frederic Renschler; Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare/TGen, Scottsdale, AZ; Florida Cancer Specialists, Englewood, FL; Arena Oncology Associates, Lake Success, NY; University of Washington, Seattle, WA; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Princess Margaret Hospital, Toronto, ON, Canada; Atlanta Cancer Care, Atlanta, GA; N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia; Roswell Park Cancer Institute, Buffalo, NY; Georgia Cancer Specialists PC, Atlanta, GA; Southern Health, East Bentleigh, VIC, Australia; Ospedale San Raffaele, Istituto di Ricovero e Cura a Carattere Scientifico, Milan, Italy; Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ; Vall d'Hebron University Hospital, Barcelona, Spain; Centro Integral Oncológico Clara Campal, Madrid, Spain; University Hospitals Leuven, Leuven, Belgium; Prince of Wales Hospital, Sydney, Australia; Celgene Corporation, Summit, NJ; Bionomics Ltd., Thebarton, Australia

Background: *nab*-paclitaxel (*nab*-P; 130 nm albumin-bound paclitaxel) has demonstrated both single-agent activity and synergy with gemcitabine (G) in preclinical models of pancreatic cancer (PC). *nab*-P + G also demonstrated promising efficacy in a phase I/II study in metastatic PC (*J Clin Oncol.* 2011:4548-4554), warranting a phase III study of *nab*-P + G vs G for metastatic PC. **Methods:** 861 patients (pts) with metastatic PC and a Karnofsky performance status (KPS) ≥ 70 were randomized at 151 community and academic centers 1:1 to receive *nab*-P 125 mg/m^2 + G 1000 mg/m^2 days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^{2}weekly for 7 weeks followed by 1 week of rest (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle ≥ 2). The primary endpoint was OS; secondary endpoints were PFS and ORR by independent review. **Results:** The median age was 63 years (range 27 - 88). KPS was 100 (16%), 90 (44%), 80 (32%), and 70 (7%). Pts had advanced disease with liver metastases (84%), ≥ 3 metastatic sites (46%), and CA19-9 ≥ 59 × ULN (46%). *nab*-P + G was superior to G for all efficacy endpoints: median OS was 8.5 vs. 6.7 mo (HR 0.72; 95% CI, 0.617 - 0.835; *P* = 0.000015); median PFS was 5.5 vs. 3.7 mo (HR 0.69; 95% CI, 0.581 - 0.821; *P* = 0.000024), and ORR was 23% vs. 7% (*P* = 1.1 × 10^{-10}) by RECIST v1.0. Metabolic response by PET in 257 patients was 63% for *nab*-P + G vs 38% for G (*P* = 0.000051). CA19-9 response (≥ 90% decrease) was 31% for *nab*-P + G vs. 14% for G (*P* < 0.0001). Grade ≥ 3 AEs with *nab*-P + G vs. G included neutropenia (38% vs. 27%), fatigue (17 % vs. 7%), diarrhea (6% vs 1%), and febrile neutropenia (3% vs. 1%). Grade ≥ 3 peripheral neuropathy (PN) occurred in 17% vs. 1% of pts who received *nab*-P + G vs. G, respectively; for *nab*-P + G, PN improved to grade ≤ 1 in a median 29 days, and 44% of patients resumed *nab*-P treatment. The median duration of treatment was 3.9 mo for *nab*-P + G and 2.8 mo for G. **Conclusions:** MPACT was a large, international study performed at community and academic centers. *nab*-P + G was superior to G across all efficacy endpoints, had an acceptable toxicity profile, and is a new standard for the treatment of metastatic PC that could become the backbone for new regimens. Clinical trial information: NCT00844649.

GENITOURINARY CANCER

Guru Sonpavde, M.D.

NOTES

GURU SONPAVDE, M.D. SLIDES
GENITOURINARY CANCERS

GU cancers ASCO 2013 update

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Recent Trials in mCRPC: OS

Therapy	Disease State	Comparator	Hazard Ratio	P value
Sipuleucel-T *(2010)*	**Chemo-näive# (mostly)**	**Placebo**	**0.775**	**0.032**
Cabazitaxel *(2010)*	**Post-Docetaxel**	**Mitoxantrone**	**0.70**	**<0.0001**
Abiraterone acetate *(2011, 2012)*	**Post-Docetaxel**	**Placebo**	**0.646**	**<0.0001**
	Chemo-naïve	**Placebo**	**0.75**	**0.0097***
Enzalutamide *(2012)*	**Post-Docetaxel**	**Placebo**	**0.631**	**<0.001**
Radium-223 *(2013)*	**Post-Docetaxel (or non-chemo)**	**Placebo**	**0.70**	**0.002**

#minimally sx or asx

*not statistically significant

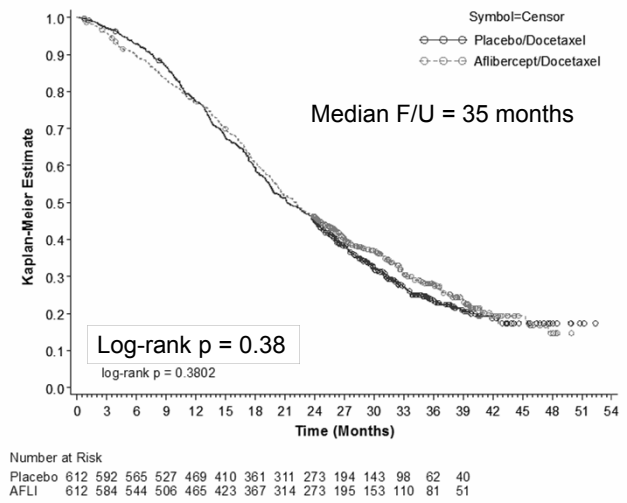
Three major drug development spaces have emerged for mCRPC

- Pre-docetaxel
  - Non-metastatic (M0) CRPC disease
  - Metastatic but asymptomatic/mildly symptomatic
    - Sipuleucel-T
    - Abiraterone acetate
- With docetaxel in mCRPC
  - No successes in this space yet!
- After docetaxel in mCRPC
  - Cabazitaxel, Abiraterone, Enzalutamide, Alpharadin

AFLIBERCEPT VERSUS PLACEBO WITH DOCETAXEL/PREDNISONE FOR METASTATIC CRPC: VENICE PHASE III TRIAL

Ian Tannock, Karim Fizazi, Sergey Ivanov, Camilla Thellenberg Karlsson, Aude Flechon, Iwona Skoneczna, Francisco Orlandi, Gwenaelle Gravis, Vsevolod Matveev, Sevil Bavbek, Thierry Gil, Luciano Viana, Osvaldo Arén, Oleg Karyakin, Tony Elliott, Alison Birtle, Emmanuelle Magherini, Laurence Hatteville, Daniel Petrylak, Bertrand Tombal, Mark Rosenthal, on behalf of the VENICE investigators

VENICE TRIAL: overall survival



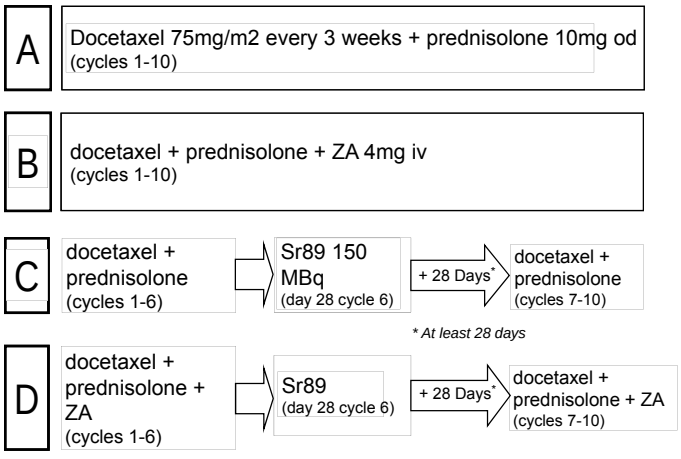
Negative phase III trials of combinations with docetaxel

Trial	Partner	Therapeutic target
ASCENT II	DN101 (calcitriol)	Vitamin D
VITAL II	GVAX vaccine	Immunotherapy
SWOG S0421	Atrasentan	Endothelin receptor
ENTHUSE	Zibotentan	Endothelin receptor
MAINSAIL	Lenalidomide	Antiangiogenic, Immune-modulation
CALGB 90401	Bevacizumab	VEGF
READY	Dasatinib	Src
VENICE	Aflibercept	VEGF, PLGF

STRONTIUM-89 AND ZOLEDRONIC ACID IN CASTRATE-REFRACTORY PROSTATE CANCER (CRPC) METASTATIC TO BONE RECEIVING DOCETAXEL (TRAPEZE)

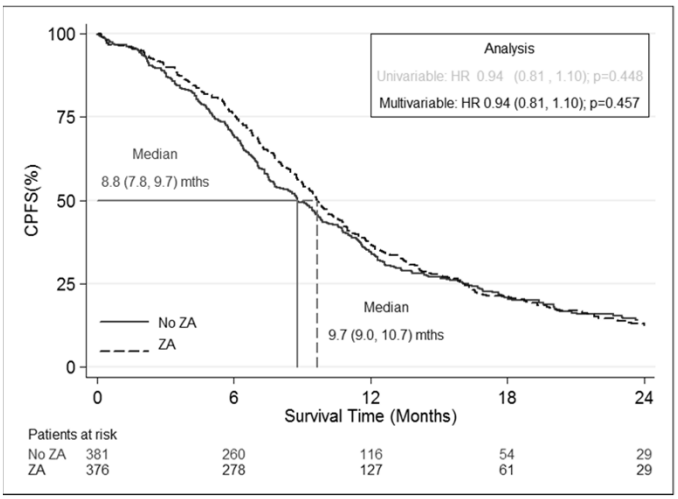
Nicholas James, Sarah Pirrie, Darren Barton, Janet Brown, Lucinda Billingham, Stuart Collins, Adam Daunton, Alison Birtle, Prabir Chakraborti, Daniel Ford, Syed Hussain, Helen Jones, Ann Pope, Emilio Porfiri, Martin Russell, Andrew Stanley, John Staffurth, Duncan McLaren, Chris Parker, James Wylie and the TRAPEZE trial investigators

TRAPEZE Phase III study treatments

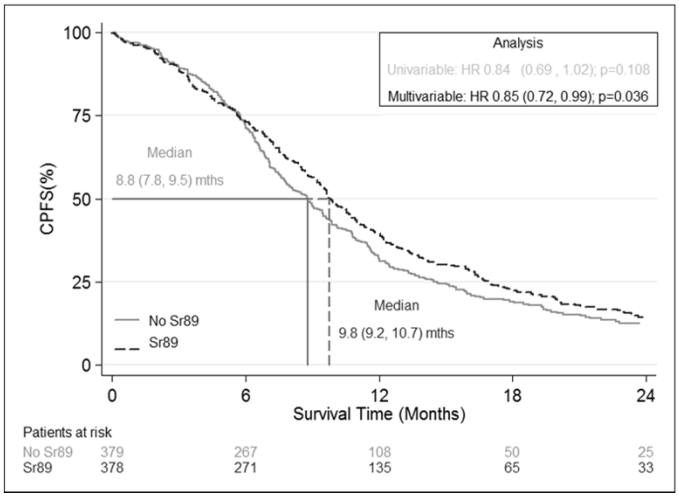


ARMS B & D : Post chemotherapy, ZA will be administered at 4-weekly intervals until protocol defined disease progression.

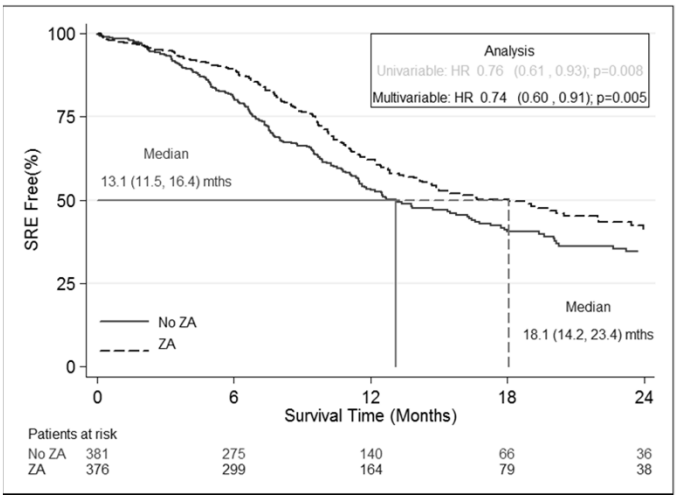
TRAPEZE Clinical progression free survival: zoledronic acid comparison



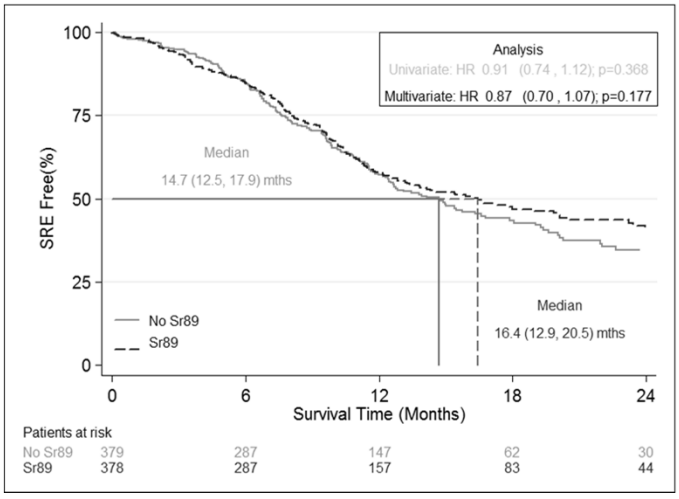
TRAPEZE: Clinical progression free survival: Sr-89 comparison



TRAPEZE: SRE free interval: ZA comparison



TRAPEZE: SRE free interval: Sr-89 comparison



Takeaways: TRAPEZE trial

- Neither zoledronic acid nor strontium
  - improved survival
  - impact on progression-free survival
- Zoledronic acid's effect on clinical SREs was confirmed in the context of docetaxel chemotherapy
  - The use of clinical SREs or SSEs (symptomatic skeletal events) is desirable
- The cost effectiveness of SRE prevention compared to SRE treatment needs analysis
- will alpharadin perform better?

EFFECT OF CORTICOSTEROID USE AT BASELINE ON OVERALL SURVIVAL IN PATIENTS RECEIVING ABIRATERONE ACETATE: RESULTS FROM A RANDOMIZED STUDY (COU-AA-301) IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER POST-DOCETAXEL

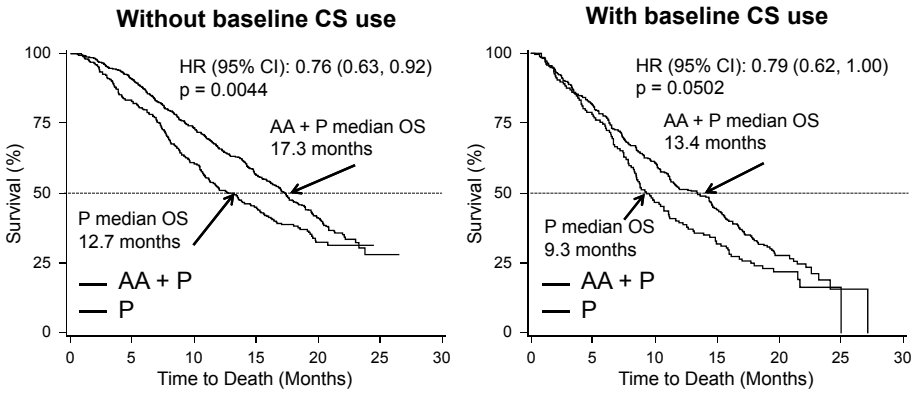
R. Bruce Montgomery, Thian Kheoh, Arturo Molina, Jinhui Li, Joaquim Bellmunt, Charles J. Ryan, NamPhuong Tran, Yohann Loriot, Eleni Efstathiou, Howard I. Scher, Johann S. de Bono

Activity of corticosteroids in prostate cancer

Study	N	Corticosteroid	Response rate to CS
Tannock I, et al. *JCO*. 1996;14:1756	81	Pred 10 QD *vs. mito/pred*	22% PSA response
Storlie JA, et al. *Cancer*. 1995;76:96	38	Dexamethasone 0.75 mg BID	79% w/improved sxs - 63% PSA response
Venkitaraman R, et al. *BJU Int*. 2008;101:440	102	Dexamethasone 0.5 mg QD	49% PSA response 11.6 mo duration
de Bono JS, et al. *NEJM*. 2011;364:1995	398	COU-AA-301 – Prednisone/ prednisolone 5 mg BID	10% PSA response 3% RECIST response
Ryan CJ, et al. *NEJM*. 2013;368:138	542	COU-AA-302 – Prednisone 5 mg BID	24% PSA response rate 16% RECIST response

However: Analysis of the AFFIRM phase III trial (enzalutamide vs. placebo in CRPC) suggested that prior steroid use was independently associated with a poorer prognosis

Overall survival by steroid use at baseline

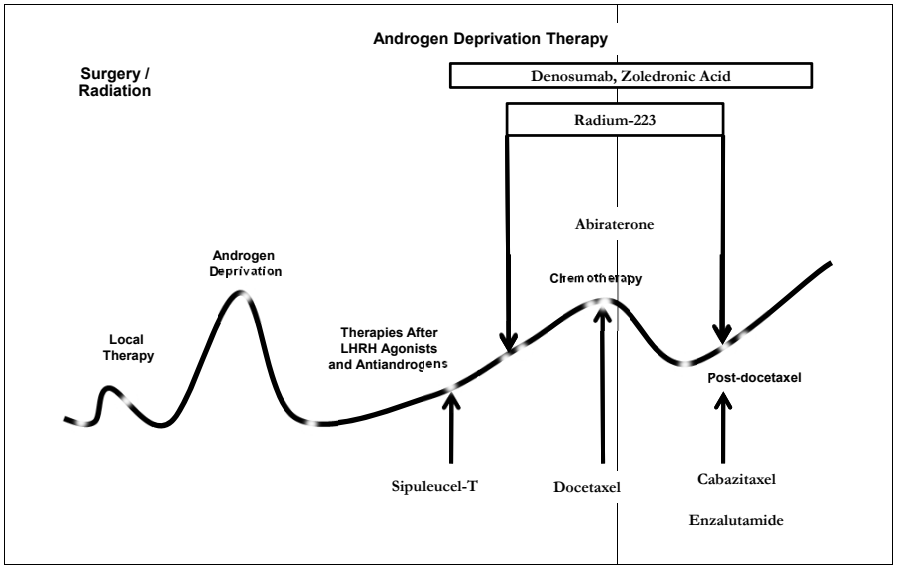


Corticosteroid use was <u>not</u> an independent adverse prognostic factor. Instead, its use was associated with other factors that associate with worse prognosis

Takeaways: Corticosteroid use in mCRPC

- In this study, corticosteroid use was not independently prognostic
- This result differs from a prior analysis of the AFFIRM study – why?
  - *(1) Steroids are not harmful.* Unaccounted factors could explain the relationship between steroid use and shorter survival in the AFFIRM study
    - Patients are on steroids since were more symptomatic (worse disease)?
  - *(2) Steroids are harmful.* Subsequent steroid use in all patients in COU-301 could have obscured an impact of steroids on survival
  - (3) *Steroids are harmful, but the effect is specific to androgen receptor antagonists*
    - Preclinical data (Sawyers, ASCO plenary 2013) suggest that glucocorticoid receptor upregulation and activation may be one mechanism for enzalutamide resistance

Treatment Landscape: mCRPC



Ongoing Phase III Trials in CRPC

- **Immunotherapy**
  - Palliative XRT +/- ipilimumab (CTLA-4 blockade), pre or post-docetaxel
  - Metastatic hormone sensitive PCa: ADT +/- Sipuleucel-T
  - Pox-virus based anti-PSA agent (prostvac®) for chemonaive mCRPC
- **Anti-Angiogenic Therapy**
  - Tasquinimod vs placebo, pre-docetaxel phase 3 (oral S100A9 inhibitor with immunostimulatory and anti-angiogenic properties)
- **Novel Hormonal Therapies**
  - TAK700 with prednisone vs. prednisone: two phase 3 trials (pre and post-docetaxel)
  - Enzalutamide vs. placebo: 1680 (PREVAIL pre-docetaxel), ongoing
  - ARN-509 vs placebo: new AR antagonist in non-metastatic CRPC
- **Novel cytotoxics or other agents**
  - OGX-011 : Clusterin ASO, 2 phase III trials combined with docetaxel or cabazitaxel
  - Cabozantinib: c-met/VEGF2 multi-kinase inhibitor, 2 phase 3 trials post-docetaxel
  - Cabazitaxel front line vs. docetaxel (FIRSTANA trial)

Summary: Therapeutic Options for CRPC

- Current sequence of therapy for mCRPC: sipuleucel-T → Abiraterone →Docetaxel →Cabazitaxel/Enzalutamide/Radium-223→Mitoxantrone
- Ideally, biomarkers predictive for benefit will be validated, leading to better patient selection.
- In the absence of predictive biomarkers, serial administration of ALL active agents probably maximizes survival (Costs/Biases play role)
- Basic research to elucidate molecular biology is critically important (pre-eminent driver still unclear)
- <u>Clinical Trials evaluating new agents or combinations should remain priority</u>

CCP SCORE: A NOVEL GENETIC TEST FOR PROSTATE CANCER

Jack M. Cuzick, Michael K. Brawer, Matthew R. Cooperberg,
Gregory P. Swanson, Stephen J. Freedland, Julia E. Reid, Gabrielle Fisher,
Jerry S. Lanchbury, Alexander Gutin, Steven Stone, and Peter Carroll

CCP score: Methods

- Analyzed formalin-fixed prostate tissue from 5 studies of men with adenocarcinoma
- The CCP score was calculated by measuring the average RNA expression of 31 cell cycle progression genes normalized by the average expression of 15 housekeeping genes as quantitated by RT-PCR
- The CCP score hazard ratio (HR) is given for a one-unit change in score – The median size of the IQR of the CCP score in these studies was 1.1

Presented by: Jack Cuzick

CCP Score Adds Significant Prognostic Information

Study	Endpoint	Multivariate model*			
		Hazard ratio (95% CI)	CCP score p-value	PSA p-value	Gleason Score p-value
TURP conservatively managed	CaP death	**2.6 (1.9, 3.4)**	$<10^{-10}$	$<10^{-7}$	0.028
Needle Biopsy conservatively managed	CaP death	**1.7 (1.3, 2.1)**	$<10^{-4}$	0.017	0.0022
Rad Prostatectomy 1	BCR	**1.7 (1.4, 2.2)**	$<10^{-5}$	$<10^{-8}$	0.015
Rad Prostatectomy 2	BCR	**2.0 (1.4, 2.8)**	$<10^{-4}$	0.12	0.17
External Beam XRT	BCR	**2.1 (1.0, 4.2)**	0.035	0.054	0.20

* Includes additional clinical covariates

Presented by: Jack Cuzick

CCP score: Summary of Results

- CCP score was a highly significant predictor of outcome in all five studies
- CCP score was a predictor in all studies in multivariate analysis
- In all five studies, the hazard ratios (HRs) per unit of change in the CCP score were remarkably similar, ranging from 2.0 to 2.9
- These HRs indicate that the effect size for the CCP score is robust in varying clinical settings

Presented by: Jack Cuzick

CCP score: Takeaways

- CCP score is a (another) independent prognostic factor in prostate cancer
- Is it ready for clinical use?
- To help clinicians make these critical decisions we still need:
  - Diagnostic assays that improve substantially on the current prognostic/predictive models (i.e. clinical stage, PSA, Gleason's score, and others)
  - Highly robust prognostic tools – i.e. post test probability high enough to make a clinical decision based on the test
  - Predictive tools – test that predict which patients do well with distinct clinical strategies – beyond prognosis
  - Prospective validation of diagnostic tests in the context of use

Duration of androgen deprivation therapy with XRT in high risk localized prostate cancer: PCS IV trial

Abdenour Nabid[1], Nathalie Carrier[1], André-Guy Martin[2], Jean-Paul Bahary[3], Luis Souhami[4], Marie Duclos[4], François Vincent[5], Sylvie Vass[6], Boris Bahoric[7], Robert Archambault[8], Céline Lemaire[9]

[1] Centre Hospitalier Universitaire de Sherbrooke, CA, [2] Centre Hospitalier Universitaire de Québec, CA, [3] Centre Hospitalier Universitaire de Montréal, CA, [4] Centre Universitaire de Santé McGill, CA, [5] Centre Hospitalier Régional de Trois-Rivières, CA, [6] Centre de Santé et Services Sociaux de Chicoutimi, CA, [7] Hôpital Général Juif de Montréal, CA, [8] Hôpital de Gatineau, CA, [9] Hôpital Maisonneuve-Rosemont de Montréal, CA

PCS IV: Inclusion criteria

- High Risk needed one of following:

- T3, T4
- PSA > 20 ng/ml,
- Gleason score > 7
- No LN or regional metastasis

PCS IV: Endpoints

Primary : Overall survival,
disease specific survival
quality of life

Secondary : Disease-free survival
biochemical failure
site of tumor relapse.

PCS IV: Randomization

Arm 1 : ADT* 36 months + RT**
(n=310) Bicalutamide 50 mg id x 1 month
Goserelin 10.8 mg q 3 months x 12

Arm 2 : ADT* 18 months + RT**
(n=320) Bicalutamide 50 mg id x 1 month
Goserelin 10.8 mg q 3 months x 6

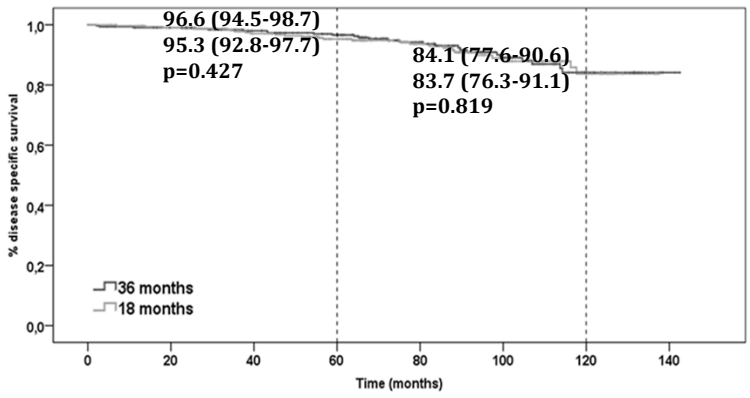
* ADT : neoadjuvant (4 months), concomitant and adjuvant to RT
** RT : pelvis 44 Gy - 4 ½ weeks, prostate 70 Gy - 7 weeks

Median follow-up 78 months

Patient characteristics

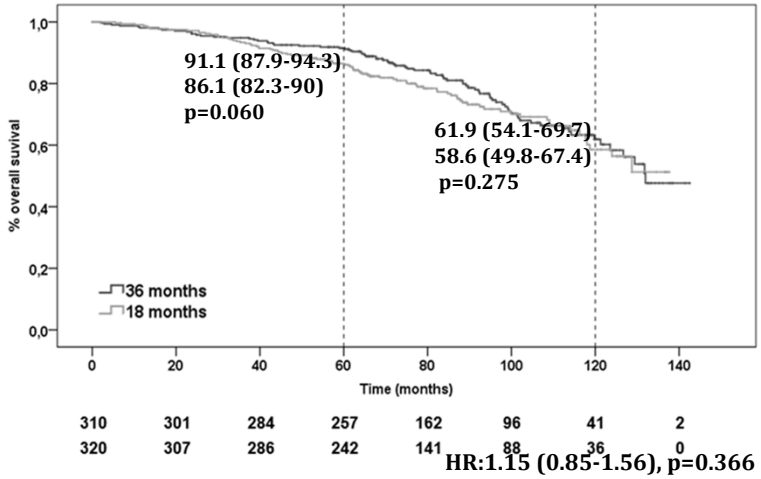
		36 months n=310	18 months n=320
Age *		**71 (66-74)**	**71 (65-74)**
PSA *		**16.6 (8.5-28.3)**	**15.4 (8.4-28.1)**
Gleason score *		**8 (7-8)**	**8 (7-8)**
Clinical stage – n (%)	**T1c**	**72 (23.2)**	**79 (24.7)**
	T2a	**60 (19.4)**	**67 (20.9)**
	T2b	**96 (31.0)**	**101 (31.6)**
	T3	**82 (26.5)**	**71 (22.2)**
	T4	**0 (0)**	**2 (0.6)**

PCS IV: Disease specific survival



HR: 1.07 (0.62-1.84), p=0.819

PCS IV: Overall Survival



HR:1.15 (0.85-1.56), p=0.366

EORTC vs. PCS IV

Study	Nb patients	Median f-up (years)	5 - year Survival (%)		
Duration of AB			6 months	18 months	36 months
EORTC [1]	970	6.4	81		84.8
PCS IV	630	6.5		86.1	91.1

[1] Bolla M et al. N Engl J Med 2009

Duration of ADT with XRT: Conclusion

In localized high risk prostate cancer :

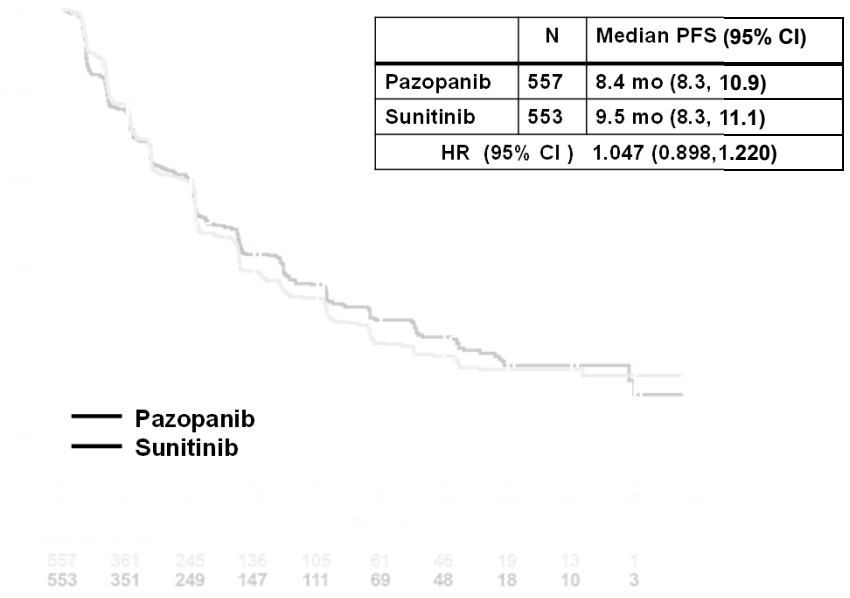
- ADT delivered during 18 months could represent a threshold effect with no further gain with longer duration.
- Duration of side effects and treatment costs can be significantly reduced

Treatment impact on quality of life is now under analysis

RCC therapy algorithm

Setting	Patients	Therapies with level 1 evidence	Other Options
First Line	Good or intermediate risk	Sunitinib Pazopanib Bevacizumab+IFN	High dose IL-2 in highly select patients Sorafenib Clinical Trial Observation in select patients
	Poor risk	Temsirolimus	Other VEGF inhibitors Clinical Trial
Second Line	Prior cytokines	Sorafenib Axitinib Pazopanib	Sunitinib Clinical Trial
	Prior VEGFi	Axitinib Everolimus	Targeted therapy not previously used
	Prior mTORi	No data	Axitinib
Third Line	Prior VEGFi	Everolimus	Targeted therapy not previously used

Pazopanib vs. Sunitinib as first-line therapy
COMPARZ trial: Motzer RJ, ESMO 2012



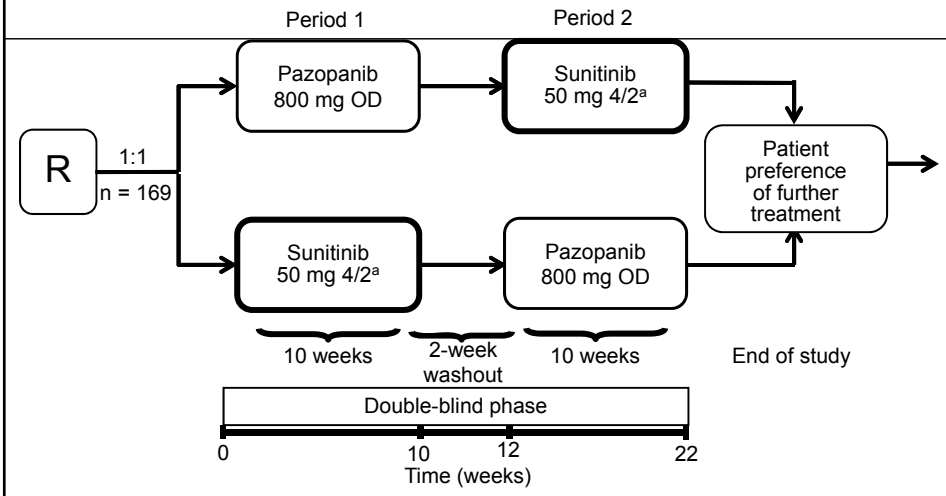
	N	Median PFS (95% CI)
Pazopanib	557	8.4 mo (8.3, 10.9)
Sunitinib	553	9.5 mo (8.3, 11.1)
HR (95% CI)		1.047 (0.898,1.220)

COMPARZ trial: Common Adverse Events

	Pazopanib (n = 554) %	Sunitinib (n = 548) %
Adverse Event [1]	**All Grades**	**All Grades**
Any event [2]	>99	>99
Diarrhea	63	57
Fatigue	55	63
Hypertension	46	41
Nausea	45	46
Decreased appetite	37	37
ALT increased	31	18
Hair color changes	30	10
Hand-foot syndrome	29	50
Taste alteration	26	36
Thrombocytopenia	10	34

[1] AE ≥30% in either arm
[2] 2% of patients in pazopanib arm and 3% of patients in sunitinib arm had grade 5 adverse events
Blue Highlight: Risk greater for sunitinib and 95% CI for relative risk does not cross 1

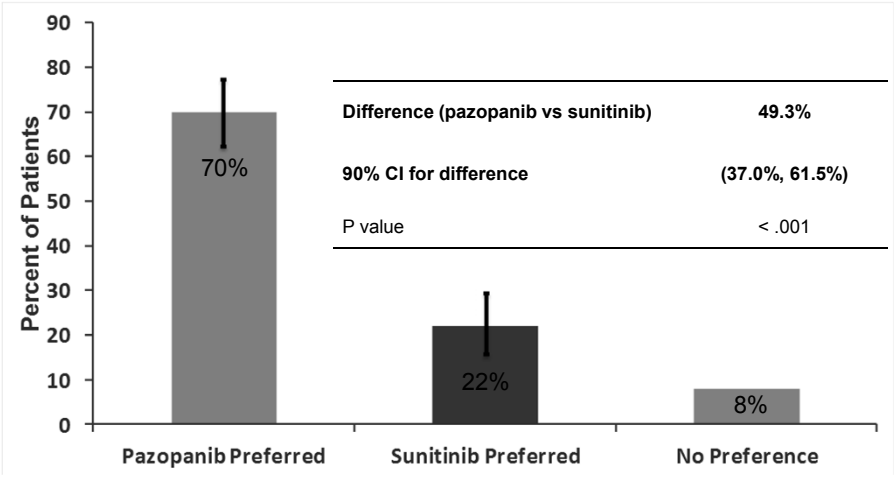
PISCES Design



Stratification factors:
- ECOG PS (0 vs 1)
- Metastatic sites (1 vs ≥ 2)

Escudier ASCO 2012

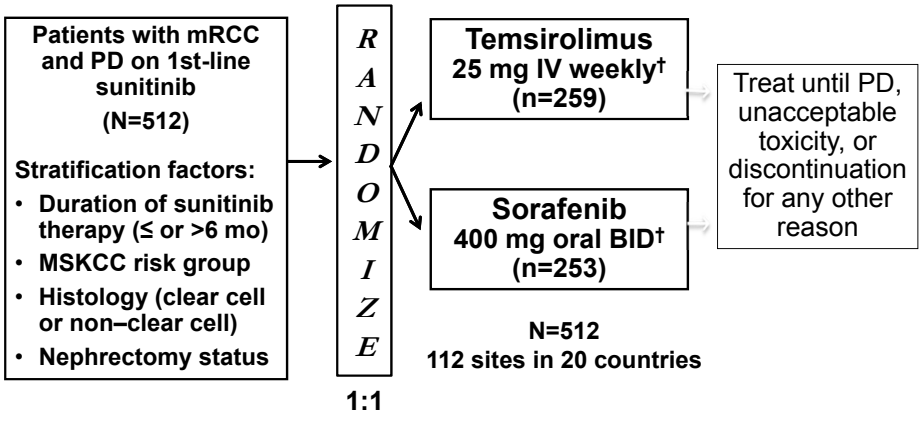
PISCES trial: Patient Preference



Escudier ASCO 2012

Abbreviation: CI, confidence interval.

INTORSECT*: Hutson, Escudier, ESMO 2012

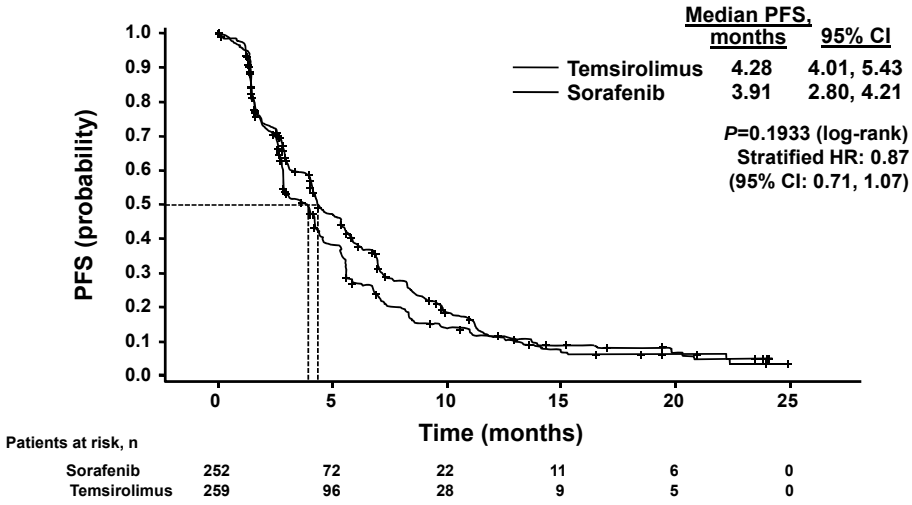


First patient randomized: September 25, 2007; last patient randomized: January 31, 2012.
Data cutoff: May 4, 2012. At present, 2 patients are on study.

*ClinicalTrials.gov Identifier: NCT00474786.
†Dose reductions were allowed: temsirolimus (to 20 mg then 15 mg); sorafenib (to 400 mg/day then every other day).

BID, twice daily; IRC, independent review committee; IV, intravenous; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; PD, progressive disease; PFS, progression-free survival.

INTORSECT: Progression-Free Survival

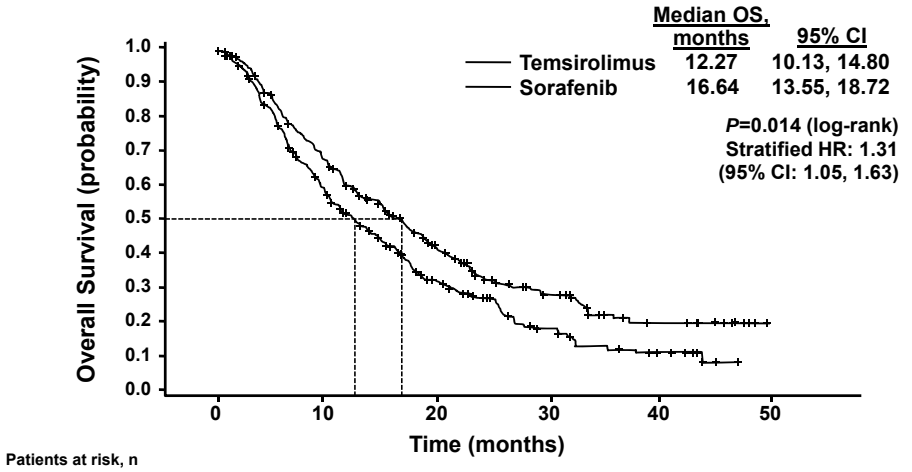


Patients at risk, n

Sorafenib	252	72	22	11	6	0
Temsirolimus	259	96	28	9	5	0

CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; PFS, progression-free survival.

INTORSECT: Overall Survival

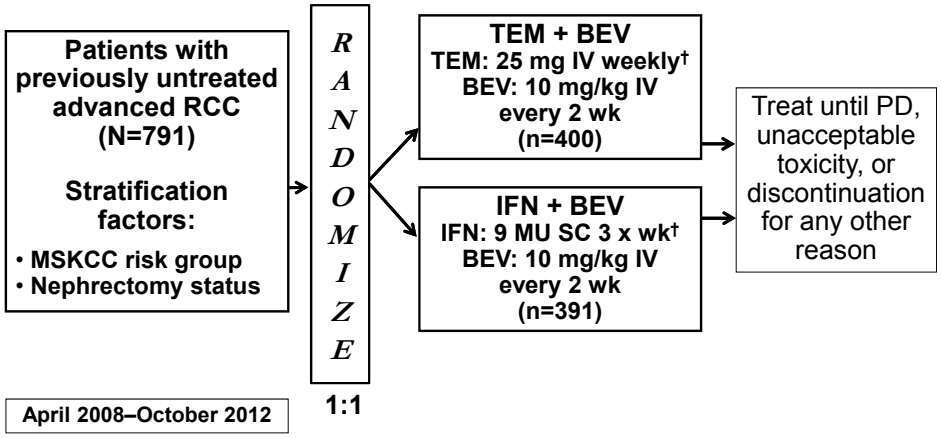


Patients at risk, n

Sorafenib	253	158	74	34	13	0
Temsirolimus	259	132	54	22	8	0

CI, confidence interval; HR, hazard ratio; OS, overall survival.

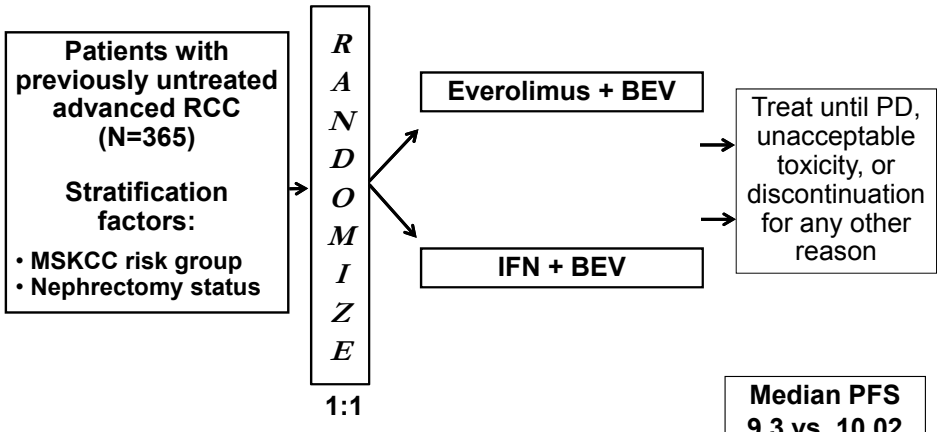
INTORACT* Study Design
Rini BI, ESMO 2012



*ClinicalTrials.gov Identifier: NCT00631371
†Dose reductions were allowed for TEM and IFN, but not for BEV

BEV, bevacizumab; IFN, interferon alfa; IRC, independent review committee; IV, intravenous; MSKCC, Memorial Sloan-Kettering Cancer Center; PFS, progression-free survival; RCC, renal cell carcinoma; SC, subcutaneously; TEM, temsirolimus.

First-line R-II of Bev-IFN vs. Bev-Everolimus
RECORD-2: Ravaud A, ESMO 2012



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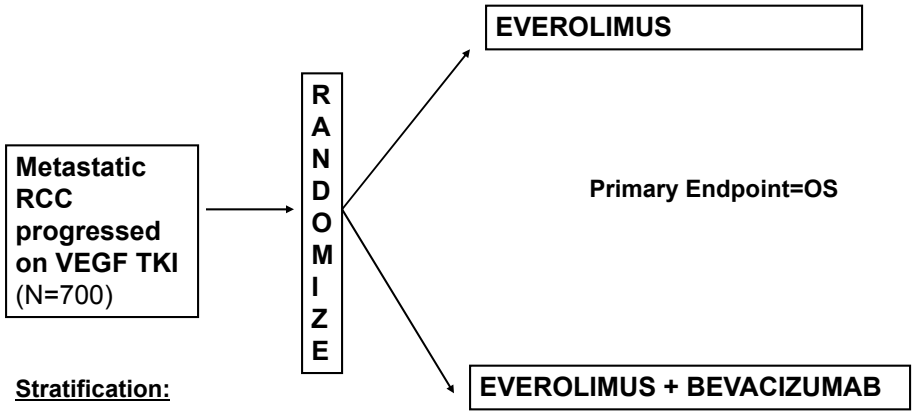
VEGF + mTOR inhibitor as 2nd line?

CALGB phase III trial



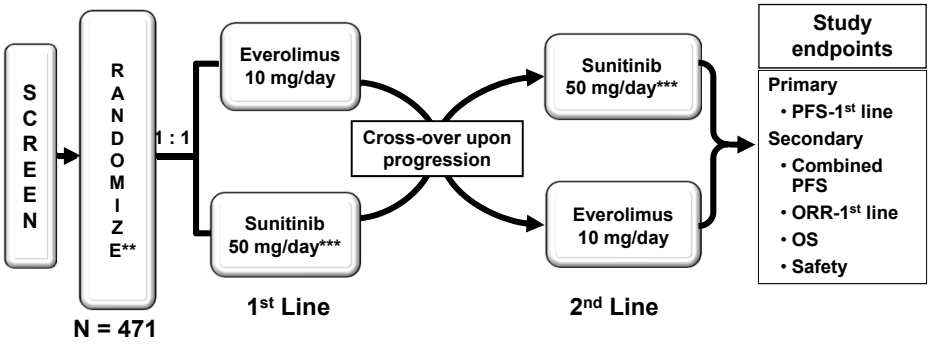
Stratification:

-Prognostic Risk factors

-Time on VEGR TKI (< or ≥ 12 weeks)

www.clinicaltrials.gov (NCT01198158)

RECORD3: Study Design*
Motzer RJ, ASCO 2013



*NCT00903175. **Stratified by MSKCC prognostic factors. ***4 weeks on and 2 weeks off.

RECORD3: Study Objectives

- Primary objective
  - Assess PFS non-inferiority of first-line everolimus compared with first-line sunitinib
- Secondary objectives
  - Compare combined PFS* for the two sequences of treatment
  - Objective response rate (ORR)
  - Overall survival (OS)
  - Safety
  - Patient reported outcomes**
  - Tumor and blood biomarker analyses**

*Time from randomization to progression following second-line treatment or death (any time).
**Not being presented at this time.

RECORD3: Inclusion Criteria

- Metastatic RCC (clear cell or non-clear cell)
- No prior systemic therapy
- With or without nephrectomy
- Measurable disease (RECIST v. 1.0)
- KPS ≥70%
- Adequate organ function

RECORD3: Statistical Considerations

- First-line PFS for non-inferiority of everolimus vs sunitinib
  - PFS defined as time from randomization to PD or death
  - Bayesian method: non-inferiority declared if observed HR ≤1.1 (1-month difference in the median first-line PFS)
- 318 first-line events needed (total 460 patients)

RECORD3: Baseline Characteristics*

	Everolimus n = 238	Sunitinib n = 233
Median age, y (range)	62 (20–89)	62 (29–84)
Men, %	70	76
Race, %		
Caucasian	69	74
Asian	19	16
Black	3	3
Other	10	7
Karnofsky PS, %		
≥ 90	66	78
80	26	19
70	8	3
Predominant tumor histology, %		
Clear cell	86	85
Non-clear cell	13	15
Missing	<1	<1

*Baseline characteristics for patients randomized to first-line therapy.

RECORD3: Baseline Characteristics*

	Everolimus n = 238	Sunitinib n = 233
Nephrectomy, %		
Yes	67	67
Metastatic sites, %		
≥2	69	67
1	31	32
0	<1	<1
Organ involvement, %		
Lung	68	69
Bone	24	21
Liver	18	16
MSKCC risk group,[1] %		
Favorable	29	30
Intermediate	56	56
Poor	15	14

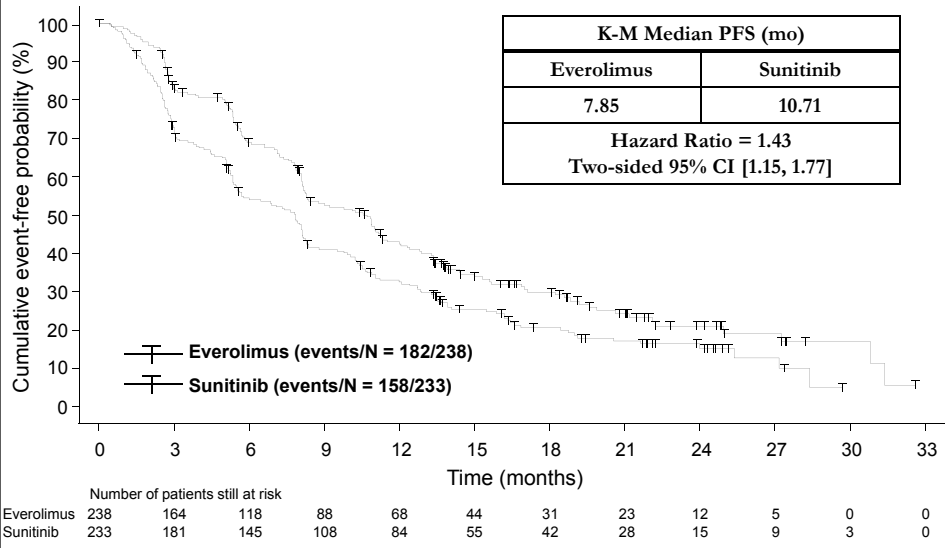
*Baseline characteristics for patients randomized to first-line therapy.
[1]Motzer RJ et al. *J Clin Oncol*. 2002;20 (1):289-296.

RECORD3: Patient flow

Randomized to treatment arm	EVE→SUN n = 238	SUN→EVE n = 233
Patients treated in first line, n	238	231*
First-line discontinuations, n (%)	201 (85)	192 (82)
Primary reasons for discontinuation, n (%)		
Progression	135 (57)	122 (52)
AEs	34 (14)	44 (19)
Death	17 (7)	9 (4)
Crossed over to second line		
Patients treated in second line, n	108	99
Second-line discontinuations, n (%)	77 (71)	75 (76)
Primary reasons for discontinuation, n (%)		
Progression	54 (50)	54 (55)
AEs	10 (9)	14 (14)
Death	4 (4)	0 (0)

*Two patients randomized to sunitinib did not receive treatment.

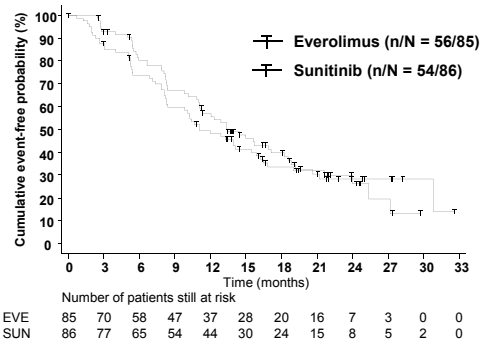
RECORD3: First-line PFS



K-M Median PFS (mo)	
Everolimus	Sunitinib
7.85	10.71
Hazard Ratio = 1.43 Two-sided 95% CI [1.15, 1.77]	

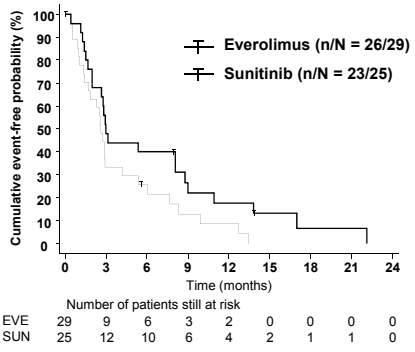
RECORD3: First-line PFS by Risk Group

MSKCC Favorable Risk



K-M Median PFS (mo)	
Everolimus	Sunitinib
11.07	13.40
Hazard Ratio = 1.20 Two-sided 95% CI [0.83, 1.75]	

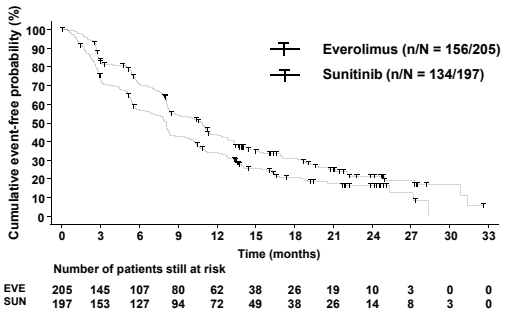
MSKCC Poor Risk



K-M Median PFS (mo)	
Everolimus	Sunitinib
2.63	2.99
Hazard Ratio = 1.73 Two-sided 95% CI [0.96, 3.12]	

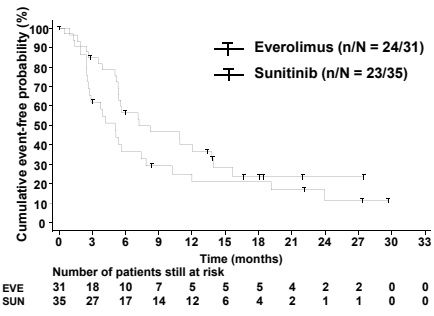
RECORD3: First-line PFS by Predominant Histology*

Clear Cell mRCC



K-M Median PFS (mo)	
Everolimus	Sunitinib
8.08	10.84
Hazard Ratio = 1.39 Two-sided 95% CI [1.10, 1.75]	

Non-Clear Cell mRCC



K-M Median PFS (mo)	
Everolimus	Sunitinib
5.09	7.23
Hazard Ratio = 1.54 Two-sided 95% CI [0.86, 2.75]	

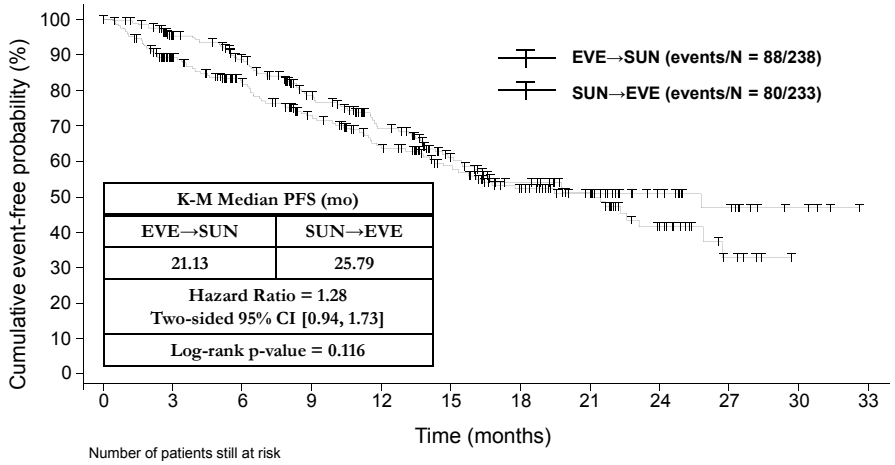
*Post-hoc exploratory sub-group analysis.

RECORD3: First-line Response Rates

	Everolimus n = 238	Sunitinib n = 233
Best overall response, n (%)		
Complete response	1 (0.4)	3 (1.3)
Partial response	18 (7.6)	59 (25.3)
Stable disease	137 (57.6)	121 (51.9)
Progressive disease	49 (20.6)	33 (14.2)
Non-evaluable	33 (13.9)	17 (7.3)
Objective response rate,* n (%) [95% CI]	19 (8.0) [4.9–12.2]	62 (26.6) [21.1–32.8]

*ORR = complete response + partial response.

RECORD3: Combined 1st and 2nd line PFS*

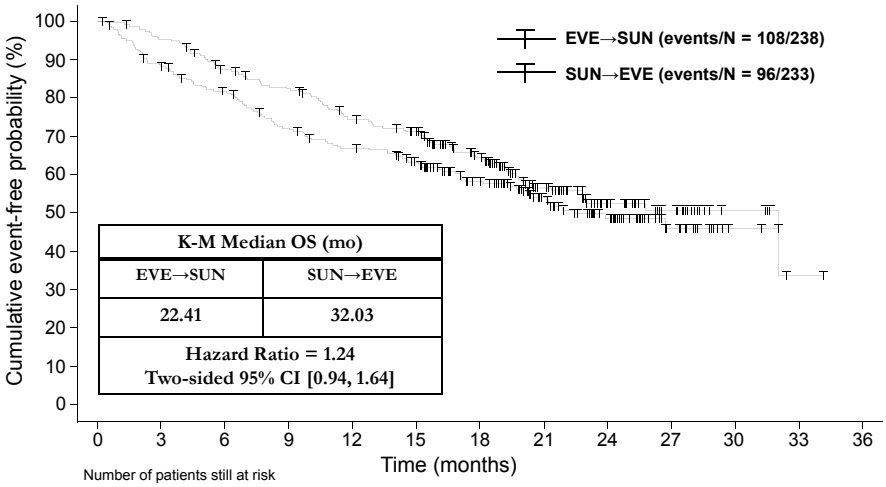


Number of patients still at risk

EVE→SUN	238	186	145	112	88	65	48	37	19	6	0	0
SUN→EVE	233	196	171	135	105	74	52	35	19	12	4	0

*Time from randomization to progression following second-line treatment or death (any time).

RECORD3: Overall Survival



Number of patients still at risk

EVE→SUN	238	208	189	165	151	137	103	66	43	15	2	0	0
SUN→EVE	233	220	198	185	164	152	115	71	38	22	6	1	0

RECORD3: Treatment Administration

Randomized to treatment arm	EVE→SUN n = 238	SUN→EVE n = 233
Patients treated in first line, n	238	231*
Median duration, mo (range)	5.6 (0-30)	8.3 (1-35)
Median relative dose intensity, %	94	85
Dose reductions, n (%)	72 (30)	117 (51)
Dose interruptions, n (%)	159 (67)	156 (68)
Crossed over to second line		
Patients treated in second line, n	108	99
Dose reductions, n (%)	40 (37)	19 (19)
Dose interruptions, n (%)	63 (58)	52 (53)

*Two patients randomized to sunitinib did not receive treatment.

RECORD3: Treatment-Emergent AEs During First-Line Therapy

AE, %	Everolimus,* n = 238		Sunitinib, n = 231	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Stomatitis	53	6/0	57	4/0
Fatigue	45	8/1	51	14/<1
Diarrhea	38	4/1	57	8/<1
Cough	38	2/0	23	<1/0
Rash	37	2/0	23	0/0
Nausea	34	2/0	49	3/0
Decreased appetite	29	3/0	34	3/0
Anemia	28	11/4	21	7/1
Peripheral edema	28	<1/0	20	1/0
Dyspnea	25	6/1	18	4/<1
Dysgeusia	21	0/0	31	0/0
Vomiting	21	2/0	30	3/<1
Constipation	19	<1/0	25	1/0
Hypertension	10	4/0	36	12/0
Hand-foot syndrome	6	<1/0	40	17/0
Thrombocytopenia	4	1/0	26	9/4

*Non-infectious pneumonitis: all grade, 7%; grade 3 and 4, 1% and <1%.
On-treatment deaths suspected to be drug related: everolimus arm, <1%; sunitinib arm, 1%.

RECORD3: Treatment-Emergent AEs During Second-Line Therapy

AE, %	Everolimus,* n = 99		Sunitinib, n = 108	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Fatigue	32	9/2	37	12/0
Anemia	26	15/0	10	3/2
Stomatitis	25	1/0	28	3/0
Decreased appetite	23	3/0	29	2/0
Dyspnea	21	5/1	14	4/0
Cough	21	1/0	11	0/0
Nausea	15	2/0	37	4/0
Diarrhea	13	1/0	46	7/0
Dysgeusia	7	0/0	23	1/0
Hypertension	3	1/0	27	12/0
Hand-foot syndrome	2	0/0	27	8/0
Vomiting	9	2/0	25	3/0
Thrombocytopenia	2	1/0	23	9/1

*Non-infectious pneumonitis: all grade, 5%; grade 3/4, 0%.

RECORD3: Conclusions

- PFS non-inferiority was not achieved for first-line everolimus compared with sunitinib
- The sequence of first-line sunitinib followed by everolimus is supported by the preliminary OS results
- Safety profile is consistent with prior experience
- Standard treatment paradigm remains first-line sunitinib followed by everolimus at progression

RECORD-3 implications for current research and practice

- First-line VEGF-targeted therapy remains standard in mRCC
- Potential uses for mTOR inhibitors as first line:
  - Temsirolimus in poor-risk disease[1]
    - -Control arm was not a TKI
  - Recent acute arterial vascular event/severe cardiomyopathy may preclude the use of a VEGF inhibitor[2,3]

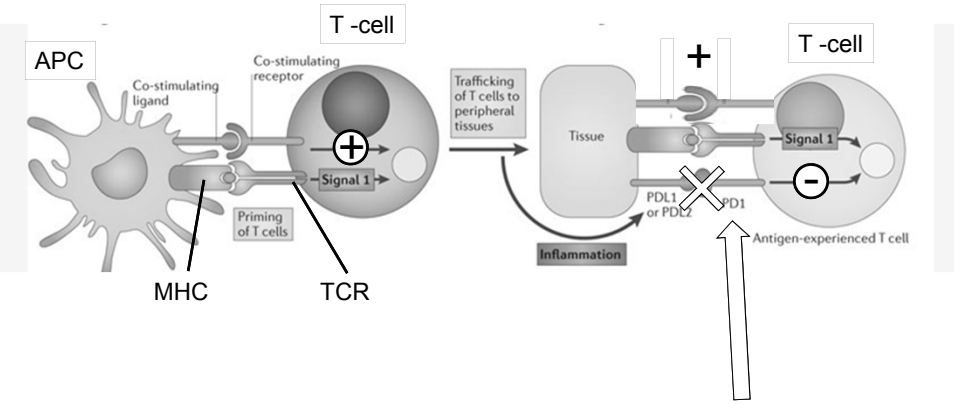
1. Hudes et al. NEJM 2007. **2**. Choueiri et al. JCO 2010. **3**. Richards et al. JCO 2011.

RECORD-3 implications for future research and practice

- Identify tumors addicted to mTOR pathway signaling:
  - Voss, Motzer and Hsieh (MSKCC): mutations along the pathway (TSC1/2, mTOR) may predict a very long TTP on mTOR inhibitors[1]
- Await results from "sequential" Phase III trials of TKI→TKI:
  - SWITCH-1 (SUN→SOR vs. SOR→SUN, n=346) [2]
  - SWITCH-2 (PAZ→SOR vs. SOR→PAZ, n=544) [3]
  - Primary endpoint of both trials: **Total PFS**
  - Preliminary safety data presented during 2012 ASCO[4]:
    - 2nd line: SOR (71/167 pts, 42%); SUN (47/167 pts, 28%)
    - Potential serious statistical flaws may limit total PFS interpretation

1. Voss et al. 11th International Kidney Cancer Symposium, 2012. **2.** http://clinicaltrials.gov/show/NCT00732914**.** **3.** http://clinicaltrials.gov/show/NCT01613846. **4.** Michel et al. ASCO 2012 (abstract 4539)

Checkpoint inhibition for RCC



Adapted from Pardoll, D. Nature Reviews Cancer, April 2012, 252

Efficacy/Safety of MPDL3280A (PD-L1 mab) in mRCC

Subgroup analysis of a large phase I (n=55)	**%**
Previously treated, non-clear cell	84%,11%
Overall Response Rate (n=47)	13%
ccRCC (n=40)	13%
nccRCC (n=6)	**17%**
PD-L1 (+)	**2/10 (20%)**
PD-L1 (-)	**2/21 (10%)**
Safety (n=55)	
Trt-related Grade 3/4	13% (none immune-related)
MTD/DLT/death on study (3-20mg/kg)	0/0/0
Fatigue, arthralgia, cough, pyrexia	35%, 33%, 27%, 26%

#4505: Clinical Activity, Safety and Biomarkers of MPDL3280A, An Engineered PD-L1 Antibody in Patients with Metastatic Renal Cell Carcinoma

Daniel Cho, Jeffrey Sosman, Mario Sznol, Michael S. Gordon, Antoine Hollebecque, Omid Hamid, David F. McDermott, Jean-Pierre Delord,Ina Rhee, Ahmad Mokatrin, Marcin Kowanetz, Roel Funke, Gregg D. Fine, Thomas Powles

		RR	24-Week PFS (K-M)	Toxicity
BMS-936558 PD-1	**RCC (n=17 @10mg/kg)**	**31%**	**67%**	14% g3-4 3/296 (1%) g5 pneumonitis
BMS-936559 PD-L1	**RCC (n=17)**	**12%**	**53%**	9% g3-4, No g5
MPDL3280A PD-L1	**RCC* (n = 47)**	**13%**	**53%**	13% g3-4– non immune No G5 Fever (35%), arthralgia (33) Cough (27), Pyrexia (26) GI (22)
	Clear cell (n = 40)	**13%**	**57%**	
	Non-clear cell (n = 6)	**17%**	**20%**	

Drake #4515 BMS-936558 – median response 12.9m, 5/10 responses for >1 year

Presented by:

MPDL3280A implications for <u>future</u> research and practice

- More mature data:
  - Late responders, PFS, 1 and 2-year OS
  - Refinement of PD-L1 biomarker and non-clear cell data
- Combination strategies:
  - Other immune checkpoint inhibitors (CTLA-4, LAG3)[1]
  - VEGF-targeted therapies: VEGF TKI, or bevacizumab (same sponsor)
  - <u>Proposal:</u> BEV+/- MPDL3280A stratified by PDL-1 status/Risk groups
- Biomarker developments:
  - PDL1 (+): higher benefit from a IL-2 immunotherapy
  - PDL1 (+): lower benefit from a VEGF TKI[2]
  - SOP for a unified PDL-1 IHC stain is needed!

1. Woo and Drake. Cancer Res, 2012. **2.** Bailey et al. ASCO 2013 (abstract 4521)

Presented by: Toni K. Choueiri, MD

#4507: ARISER: A randomized double blind phase III study to evaluate adjuvant cG250 treatment versus placebo in patients with high-risk ccRCC—Results and implications for adjuvant clinical trials. Arie S. Belldegrun, Karim Chamie, Pia Kloepfer, Barbara Fall, Paul Bevan, Stephan Störkel, Olaf Wilhelm, Allan J. Pantuck

Eligibility criteria:
1) T3/T4 N0/M0
2) any T stage and N+/M0;
3) T1b/T2 N0/M0 high-grade ccRCC

R

1:1

n = 864

cG250
50mg IV loading dose
20mg/week x 23 wks

Placebo x 24 weeks

Carbonic anhydrase IX

Enzyme catalyzes conversion of CO_2 to HCO_3-

Present on 94% of clear cell RCC

Expression is induced by HIF-a

WX-G250 is IgG1 binds to CAIX induced ADCC

WX-G250 – phase II

Phase II (n=36) OS=15 mos, 1CR, 1PR, 8SD (Bleumer BJC 2004)

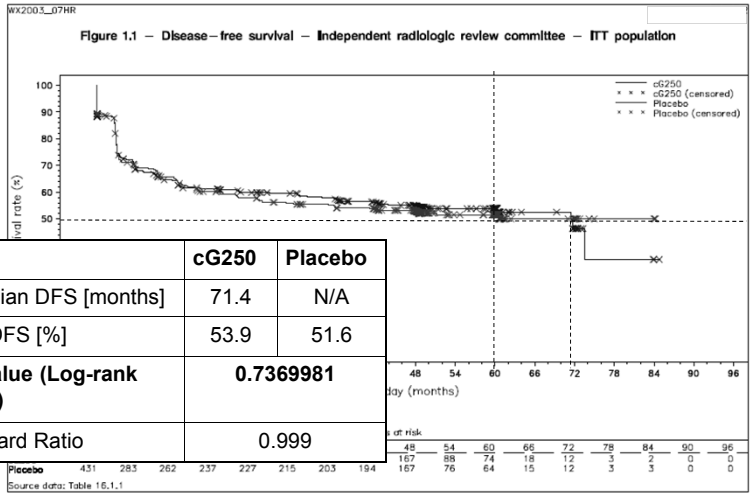
Phase II +IFN (n= 31) OS=30 mos 2PR, 9 SD> 24 wks (Siebels World J Urol 2011)

Phase III (n=864)

Superiority trial to detect

- 35% improvement in DFS
- 30% improvement in OS at 5 years
- Analysis for efficacy after 360 local DFS events with a power of 80%, and an α=0.05

ARISER: A randomized double blind phase III study to evaluate adjuvant cG250 treatment versus placebo in patients with high-risk ccRCC

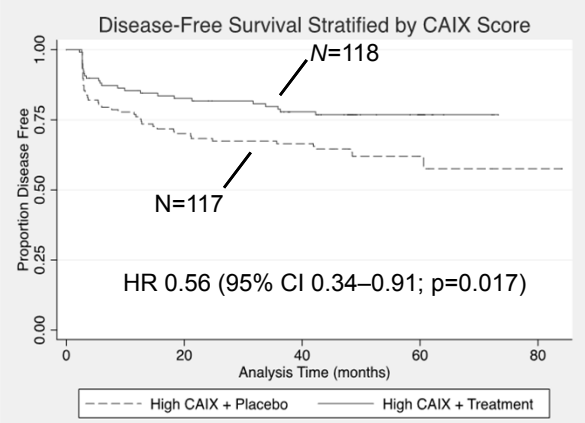


ITT	cG250	Placebo
Median DFS [months]	71.4	N/A
5y DFS [%]	53.9	51.6
p-value (Log-rank test)	**0.7369981**	
Hazard Ratio	0.999	

PRESENTED BY: M. De Santis

ARISER: Exploratory Analysis :High CAIX Score (>260)

CAIX Score (range: 0 – 300): Percent positive (0–100%) x Staining Intensity (1–3)



A phase III trial of personalized chemotherapy based on tumor marker decline in poor-prognosis germ-cell tumors (GCT): GETUG 13

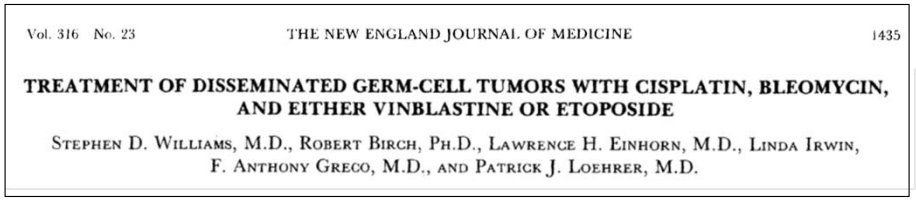
Karim Fizazi, Lance Pagliaro, Aude Flechon, Josef Mardiak, Lionnel Geoffrois, Pierre Kerbrat, Christine Chevreau, Remy Delva, Frederic Rolland, Christine Theodore, Guilhem Roubaud, Gwenaëlle Gravis, Jean-Christophe Eymard, Jean-Pierre Malhaire, Claude Linassier, Muriel Habibian, Florence Journeau, Christopher Logothetis, Stephane Culine, Agnes Laplanche

Definition of poor-prognosis GCT (IGCCCG)

- Advanced non-seminoma and:
  - Elevated serum tumor markers:
    - hCG> 50 000
    - AFP> 10 000
    - LDH> 10 x N
  - Non-pulmonary visceral metastases
  - Primary mediastinal NSGCT
- 5-year PFS: **41%;** 5-year OS: **48%**

IGCCCG, J Clin Oncol 1997, 15: 594-603

Poor-risk GCT: BEP x 4 established in 1987



Vol. 316 No. 23 THE NEW ENGLAND JOURNAL OF MEDICINE 1435

TREATMENT OF DISSEMINATED GERM-CELL TUMORS WITH CISPLATIN, BLEOMYCIN, AND EITHER VINBLASTINE OR ETOPOSIDE

STEPHEN D. WILLIAMS, M.D., ROBERT BIRCH, PH.D., LAWRENCE H. EINHORN, M.D., LINDA IRWIN, F. ANTHONY GRECO, M.D., AND PATRICK J. LOEHRER, M.D.

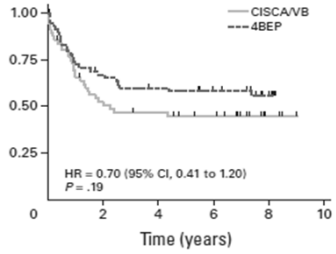
- 4 BEP > 4 PVB:
  - DFS ($p<0.05$) and OS ($p<0.05$)
  - Better tolerance (neurotoxicity)

→ **4 BEP= standard**

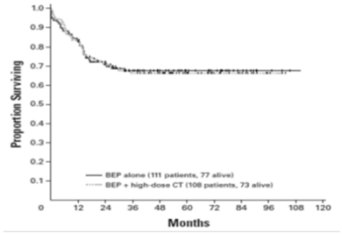
Poor-risk GCT: 25 years of negative phase 3 trials

VIP: Nichols, J Clin Oncol 1998, 16: 1287-93

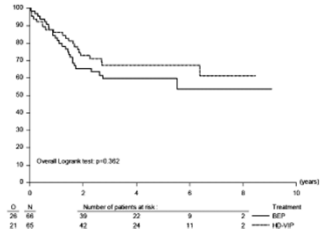
CISCA/VB: Culine, J Clin Oncol 2007, 26: 421-7



HD: Motzer, J Clin Oncol 2007; 25: 247-256

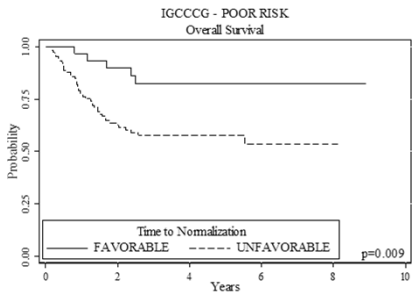


HD: Daugaard, Ann Oncol 2011; 22: 1054-61



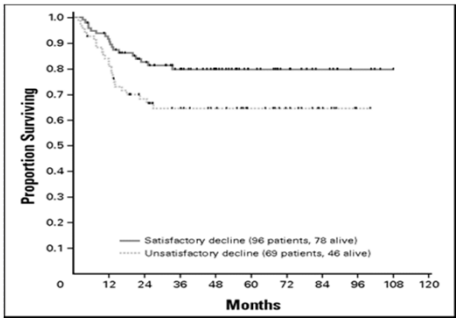
Survival according to tumor marker decline in Poor-prognosis GCT

Tumor markers assessed at Day 21



Fizazi, J Clin Oncol 2004, 22: 3868-76

Tumor markers assessed at Day 42



Motzer, J Clin Oncol 2007; 25: 247-256

GETUG 13: Working hypothesis

- **Personalize treatment** :
  - Only pts with predicted poor outcome selected for experimental treatment (unfavorable tumor marker decline)
  - Individualize cumulative doses of bleomycin (DLCO/VA>65%)
- **Incremental and small (5%?) benefit from** :
  - Paclitaxel
  - Ifosfamide
  - Increased Platin dose intensity (Oxaliplatin to avoid nephrotoxicity)
- **Prevent toxic deaths** :
  - Neutropenic fever (G-CSF)
  - Secondary leukemia (etoposide=2 g/m^2)

Presented by: Karim Fizazi

GETUG 13: Dose-dense regimen

BEP × 1

Cisplatin 20 mg/m^2/d d1-5
Etoposide 100 mg/m^2/d d1-5
Bleomycin 30 u/w

Paclitaxel-BEP + Oxaliplatin
+ G-CSF
/ 3 weeks × 2 cycles

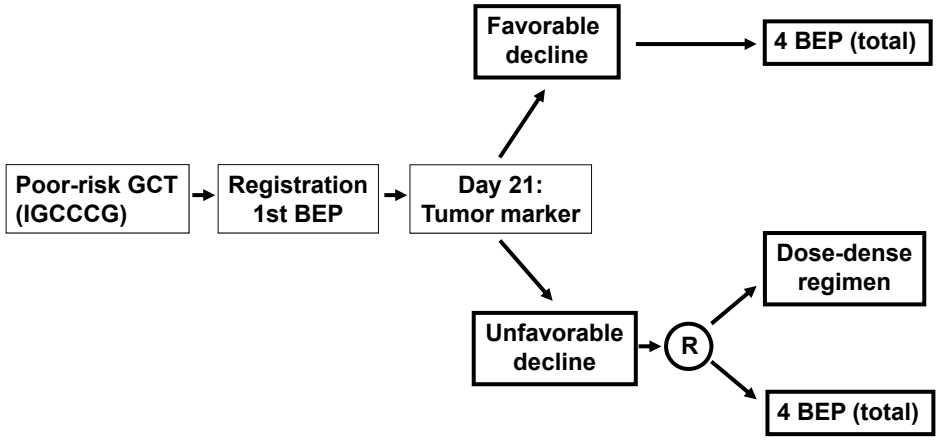
Paclitaxel 175 mg/m^2 d1
BEP as above
Oxaliplatin 130 mg/m^2 d10
G-CSF 263 µg/d (excepted chemo days)

Cisplatin, Ifosfamide, Bleomycin
+ G-CSF
/ 3 weeks × 2 cycles

Cisplatin 100 mg/m^2 d1
Ifosfamide 2g/m^2 d10,12,14
Mesnum
Bleomycin 25 U/d d10-14 (continuous IV)
G-CSF as above

Presented by: Karim Fizazi

GETUG 13 Phase III design



Presented by: Karim Fizazi

Calculation of tumor marker decline

www.igr.fr/calculation-tumor/NSGCT.xls

POOR-RISK IGCCCG ADVANCED NON-SEMINOMATOUS GERM-CELL TUMORS :
CALCULATION OF TUMOR MARKER DECLINE (AFTER 1 CYCLE OF BEP)*

Institut de cancérologie GUSTAVE ROUSSY

Date of 1st BEP :

hCG	Value	Date
Pre-chemotherapy:		
Value at day 18-21:		

AFP	Value	Date
Pre-chemotherapy:		
Value at day 18-21:		

RUN

RESET

(*) : Fizazi K, Culine S, Kramar A, Amato RJ, Bouzy J, Chen I, Droz JP, Logothetis CJ. Early predicted time to normalization of tumor markers predicts outcome in poor-prognosis nonseminomatous germ cell tumors. J Clin Oncol 2004; 22: 3868-76.

PREDICTED OUTCOME		
	4-year Progression free survival	4-year Overall Survival
Favorable decline	64%	83%
Unfavorable decline	38%	58%

Biostatistics

- Primary endpoint: PFS
  - **3-year PFS=46% in pts with unfavorable decline treated with BEP**
  - hypothesis: 20% difference
  - type 1 error: 5%, power 80%
  - **196 randomized pts** with unfavorable decline needed
  - **240 pts** (~20% pts with favorable decline)
  - Stratification by center

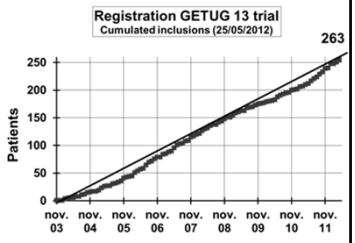
Presented by: Karim Fizazi

Key protocol items

- **Inclusion criteria**
  - All poor-risk GCT (including PS=3)
- **Conditions for next cycle dose-dense chemo:**
  - Neutrophils >1000/mm^3, Platelets $\geq$100,000 mm^3
  - Bleomycin: not administered if functional respiratory test shows a DLCO/VA report < 65%.
- **Post-chemotherapy management**
  - Surgical resection of residual masses recommended
- **Treatment at relapse**
  - Investigator's decision

Main amendements and accrual

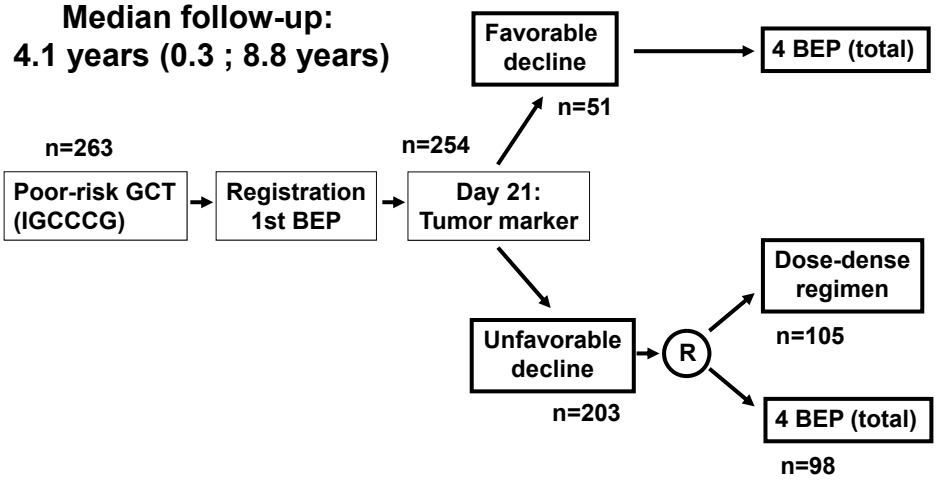
- G-CSF to be used in BEP patients
- Oxaliplatin to be deleted from cycles 3-4 of the dose-dense regimen (after first 10 pts)
- Planned number of pts: (260 instead of 240) 25% pts favorable decline vs 20% expected
- 3 countries:
  - France
  - USA
  - Slovakia



Presented by: Karim Fizazi

GETUG 13 Phase III design

Median follow-up:
4.1 years (0.3 ; 8.8 years)



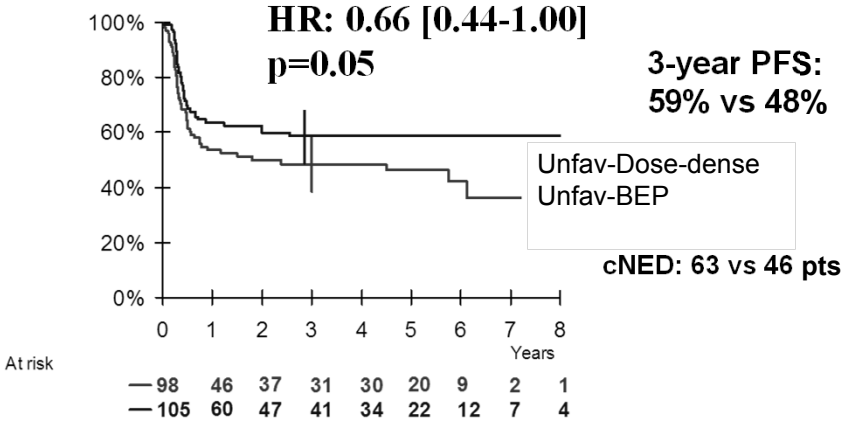
Presented by: Karim Fizazi

Patient characteristics

	Unfav BEP n=98	Dose Dense n=105	Fav BEP n=51
IGCCCG poor-prognosis	**100%**	**100%**	100%
hCG>50000 and/or AFP>10000 and/or LDH>10N	**74 (76%)**	**78 (74%)**	27 (53%)
Extra-pulmonary visceral metastases	**58 (59%)**	**59 (56%)**	32 (63%)
Primary mediastinal NSGCT	**28 (29%)**	**29 (28%)**	9 (18%)

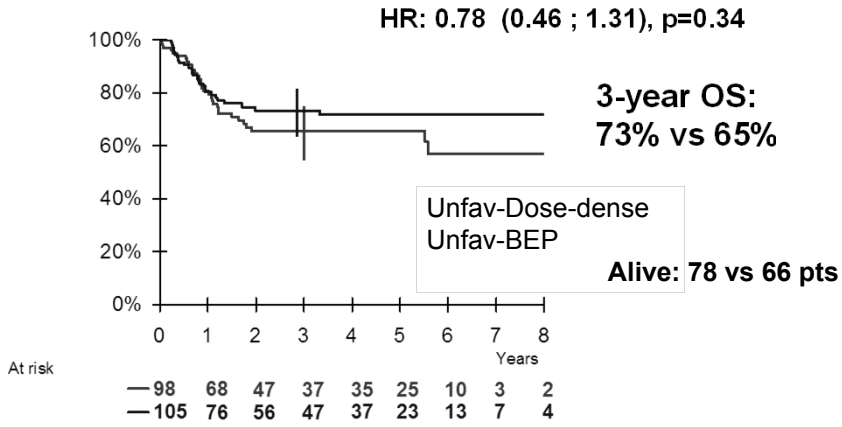
Presented by: Karim Fizazi

Primary endpoint: PFS in randomized patients with an unfavorable decline



Presented by: Karim Fizazi

OS in randomized patients with an unfavorable decline



Presented by: Karim Fizazi

Main toxicities and outcome

	Dose-dense	BEP
Neutropenic fever	17%	17%
Neurotoxicity ≥ grade 2 (mostly reversible at 2y)	23%	4%
Toxic deaths	1%	1%
Second cancers	2%	4%
Salvage HDC + transplant p=0.015	6%	16%

Presented by: Karim Fizazi

GETUG-13: Conclusion

- Dose-dense chemotherapy reduces the risk of progression or death by 34% (HR=0.66; p=0.05) in patients with slow tumor marker decline.

Early switch in chemotherapy regimen for patients with slow tumor marker decline
= New standard

Presented by: Karim Fizazi

Discussion: GETUG-13

- GETUG confirms the role of marker decline after initial chemo as significant prognostic factor in patients w/ poor risk disease
- The main benefit of the dose dense regimen appears to be the decreased need for salvage high dose chemotherapy (?)
- However the dose dense regimen is rather novel and perhaps complex (total of 6 drugs, 5 cycles of chemo) with a modest improvement in PFS no clear survival benefit
- Therefore will be important to see how this regimen is adopted over time

Observing stage I seminoma

Group	Patients	Follow up	Replase	CSS
Denmark (Daugaard 2003)	394	60	17.5%	100%
Spain (Germa-Lluch 2002)	233	33	16%	100
Denmark (Von der Masse 1993)	261	48	18.8%	98.9
Canada (Leung 2010)	484	79	15%	99.7

Adapted from Chung, JNCI 2011

Why do we need more data?

OLD HABITS DIE SLOWLY!!!
Internet survey of 261 radiation oncologists[1]

- 62% would give RT
- Doctors underestimate rate of secondary cancer
- 15% cumulative incidence over 25 years (2.6x risk) [2]

1) Arvold IJROBP 2011, p383 2) van den Belt-Dusebout JCO 2007, p4370

#4502 A nationwide cohort study of surveillance for stage I seminoma:
Mette S. Mortensen, Maria G. Gundgaard, Jakob Lauritsen, Mads Agerbæk, Niels V. Holm, Hans von der Maase & Gedske Daugaard

- Nationwide cohort
- 1,822 patients stage I seminoma followed on surveillance
- Median follow-up was 15.4 years
- Ten year cancer specific survival 99.5%
- 19.5% (355) patients had a relapse
  - median time to relapse 13.7 months (1.2-173.7 M)
  - Relapse rate after 5 year 7.3% -erratic
- Predictive factors for relapse in multivariate analyses ($p<0.01$)
  - Invasion of blood or lymphatic vessels
  - tumor size > 4 cm
  - serum human chorionic gonadotropin > 200 IU/L
  - Rete testis invasion not significant risk on multivariable evaluation

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CONCLUSIONS

- OBSERVATION STAGE I SEMINOMA SAFE
- RELAPSE CAN BE CURED
- OBSERVATION IS 1ST CHOICE

Presented by:

Current standard for stage I NSGCT

- 60% NSGCT are stage I, prognosis excellent 98% - 100%
  - Relapse rate 26% (Kollmannsberger Ann Onc 2010:1296), LVI+ RR 51%
- 3 management options exist:

1)Surveillance

2)Adjuvant chemotherapy

48% relapse →decreased to 3% relapse at 5 yrs (Tandstad JCO 2009)

3) RPLND

experience needed! Giving chemotherapy only when necessary

Active surveillance is not universally endorsed due to

- concerns about outcomes (later, more advanced relapse)
- concerns about compliance
- favoring pre-emptive strategies in high risk population
- current surveillance and follow-up schedules are empiric

Presented by:

#4503: Characterization of relapse in patients with clinical stage I (CSI) nonseminoma (NS-TC) managed with active surveillance (AS): A large multi-center study Kollmannsberger et al.

C. Kollmannsberger, T. Tandstad, P. L. Bedard, M. A. Jewett, G.Cohn-Cedermark, T. Powles, P. W. Chung, G. Daugaard, P. R. Warde, M. J.Moore, and C. R. Nichols

- Clinical stage I NS managed with "Active Surveillance"
- 6 Centers with standardized management policy

	N	Median Time To Relapse
Total	1168 (1999-2009)	
LVI-	903 (77%)	
LVI+	244 (21%)	
Good IGCCCG stage @ relapse	231 (90%)	
Relapse LVI -	129/903 (14%)	8 months (93% @3y)
Relapse LVI +	117/244 (48%)	5 months (95% @2y)

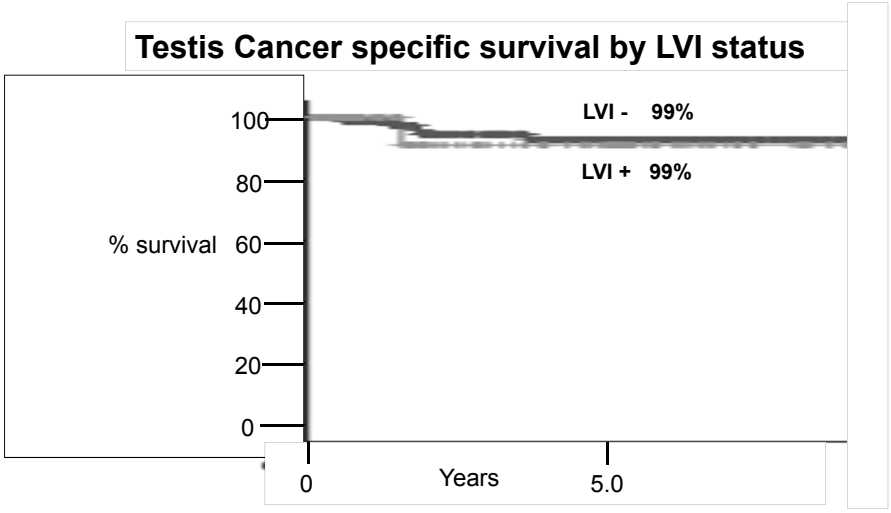
Late relapse

Relapse >2 years – erratic, no pattern

Death from disease/advanced stage relapse not correlated with "late" relapse

Relapse > 2 years on active surveillance well manageable with standard treatment

Results: Overall Outcome



Presented by:

Conclusions: Surveillance for stage 1 NSGCT

- Active surveillance is a safe and effective management option for CSI-NS-TC irrespective of risk status (author)
- Study does not change current options of surveillance, RPLND, chemotherapy
- Possible that follow up schedule of follow up can be reduced
  - LVI+ 6 CT scans over 24 months, 5 xray to 30 months, ? 60 month CT
  - LVI- 6 CT scans over 36 months, 6 xray to 36 months, ? 60 month CT
  - Exam, markers to year 5
- NCCN (maximalist approach) 13 CT scans to year 6
- Additional data to change guidelines

NCCN V 1.2013 4/21/2013

Table 1 Follow-up for Stage IA, IB on Surveillance *Only*

Year	Months between H&P, markers, chest x-ray	Months between abdominal CT
1	1-2	3-4
2	2	4-6
3	3	6-12
4	4	6-12
5	6	12
6+	12	12-24

Central Nervous System

Oliver Rixe, M.D.

NOTES

Abstract: LBA2000

Title: Bevacizumab, irinotecan, and radiotherapy versus standard temozolomide and radiotherapy in newly diagnosed, MGMT-nonmethylated glioblastoma patients: First results from the randomized multicenter GLARIUS trial.

Track: Oral Abstract Session, Central Nervous System Tumors

Authors: Ulrich Herrlinger, Niklas Schaefer, Joachim Peter Steinbach, Astrid Weyerbrock, Peter Hau, Roland Goldbrunner, Franziska Friedrich, Florian Stockhammer, Florian Ringel, Christian Braun, Ralf Kohnen, Barbara Leutgeb, Claus Belka, Horst Urbach, Walter Stummer, Martin Glas; Division of Clinical Neurooncology, Department of Neurology and Center of Integrated Oncology Cologne/Bonn, University of Bonn, Bonn, Germany; Senckenberg Institute of Neurooncology, Frankfurt, Germany; Department of Neurosurgery, University of Freiburg, Freiburg, Germany; Department of Neurology and Wilhelm Sander NeuroOncology Unit, University Hospital Regensburg, Regensburg, Germany; Department of Neurosurgery, University of Cologne and Center of Integrated Oncology Cologne/Bonn, Cologne, Germany; Department of Radiation Oncology, University of Leipzig, Leipzig, Germany; Department of Neurosurgery, University of Goettingen, Goettingen, Germany; Department of Neurosurgery, Klinikum rechts der Isar Technical University of Munich, Munich, Germany; Department of General Neurology, University of Tuebingen, Tuebingen, Germany; Research Pharmaceutical Services, Inc., Nuremberg, Germany; Roche Pharma AG, Grenzach-Wyhlen, Germany; Department of Radiation Oncology, Ludwig Maximilians University Munich, Munich, Germany; Department of Radiology, Division of Neuroradiology, University of Bonn, Bonn, Germany; Department of Neurosurgery, University of Munster, Munster, Germany; Division of Clinical Neurooncology, Department of Neurology and Center of Integrated Oncology Cologne/Bonn and Stem Cell Pathologies Group, University of Bonn and Clinical Cooperation Unit Neurooncology, MediClin Robert Janker Clinic, Bonn, Germany

Background: In patients with MGMT-nonmethylated glioblastoma (GBM), primary chemotherapy with temozolomide (TMZ) is at best moderately effective. There is an urgent need for more effective therapies in this large subgroup of GBM. Since results of phase II trials with the antiangiogenic agent bevacizumab (BEV) +/- irinotecan (IRI) are promising in recurrent GBM, the GLARIUS trial explored the efficacy of BEV/IRI as compared to standard TMZ in the first-line therapy of MGMT-non-methylated GBM. **Methods:** In the randomized, multicenter, open-label GLARIUS trial, adult patients with newly diagnosed, histologically confirmed and MGMT-non-methylated GBM received local radiotherapy (RT, 30 x 2 Gy) and were randomized (2:1) for experimental therapy with BEV (10 mg/kg q2w) during RT followed by maintenance BEV (10 mg/kg q2w) + IRI (125 mg/m² q2w (without enzyme-inducing antiepileptic drugs (EIAEDs)) or 340 mg/m² (with EIAEDs)) or standard therapy with daily TMZ (75 mg/m^2) during RT followed by 6 courses of TMZ (150-200 mg/m^2/day for 5 days q4w). The primary endpoint was progression-free survival rate after 6 months (PFS-6) as determined by central neuroradiological review. **Results:** The intent-to-treat population included 170 patients (67.1% male, median age 56 years (range 25-78 years), 48.8% complete resection rate, 78.8% of patients with KPS 90% or higher); 116 patients received BEV/IRI, 54 patients had TMZ. The frequencies of adverse events in both arms of the trial were within the expected range. The PFS-6 rate was significantly higher in the BEV/IRI arm (71.1%, 95% CI 58.1-80.8%) than in the TMZ arm (26.2%, 95% CI 13.1-41.4%, $p<0.0001$ logrank test). **Conclusions:** The significant and clinically meaningful increase in the primary endpoint PFS-6 upon BEV/IRI chemotherapy suggests that BEV/IRI is superior to standard TMZ therapy in newly diagnosed MGMT-nonmethylated GBM patients. Clinical trial information: 2009-010390-21.

Abstract: 2001

Title: A randomized phase II study of bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma: The Dutch BELOB study.

Track: Oral Abstract Session, Central Nervous System Tumors

Authors: Walter Taal, Hendrika M Oosterkamp, Annemiek M.E. Walenkamp, Laurens Victor Beerepoot, Monique Hanse, J. Buter, Aafke Honkoop, Dolf Boerman, Filip Yves Francine Leon De Vos, Rob L. Jansen, Franchette W.P.J. van den Berkmortel, Dieta Brandsma, Johan M Kros, Jacoline E Bromberg, Irene van Heuvel, Marion Smits, Bronno van der Holt, Rene Vernhout, Martin J. Van Den Bent, Landelijke Werkgroep voor NeuroOncologie; Erasmus MC, Rotterdam, Netherlands; Medisch Centrum Haaglanden, Den Haag, Netherlands; Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands; St Elisabeth Hospital, Tilburg, Netherlands; Catharina Ziekenhuis, Eindhoven, Netherlands; VU University Medical Center, Amsterdam, Netherlands; Isala Kliniek, Zwolle, Netherlands; Rijnstate Ziekenhuis, Arnhem, Netherlands; Utrecht University Medical Center, Utrecht, Netherlands; Department of Medical Oncology, Maastricht University Medical Center, Maastricht, Netherlands; Atrium Medical Center, Heerlen, Netherlands; Department of Neurology, the Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands; Department of Neuropathology, Erasmus MC–Daniel den Hoed Cancer Center, Rotterdam, Netherlands

Background: Bevacizumab (BEV) is widely used in recurrent glioblastoma, alone or in combination with other agents. There is however no well-controlled trial to support the use for this indication. **Methods:** In a three-arm Dutch multicenter randomized phase II study (NTR 1929) patients were assigned to either BEV 10 mg/kg iv every 2 weeks, BEV 10 mg/kg iv every 2 weeks and 110 mg/m^2 lomustine every 6 weeks, or lomustine 110 mg/m^{2}every 6 weeks. Eligible were patients with histologically proven glioblastoma, with a first recurrence after chemo-irradiation with temozolomide, having concluded radiotherapy more than 3 months ago, with adequate bone marrow, renal and hepatic function, and WHO performance status (PS) 0-2. Primary endpoint was 9 months overall survival (OS); P_0 was set at 35% and P_1 at 55%. Progression was defined using RANO criteria. A safety review after the first 10 patients in the combination arm was preplanned. **Results:** Between December 2009 and November 2011, 153 patients were enrolled of whom 148 were considered eligible. Median age was 57 years (range, 24-77) and median WHO PS was 1. With respect to prognostic factors groups were well balanced. After review of the safety cohort the dosage lomustine in the combination arm was lowered to 90 mg/m^2 because of hematological toxicity (predominantly thrombocytopenia without symptoms). At this lower lomustine dose level the combination treatment was in general well tolerated. Outcome: see Table. **Conclusions:** In this first well-controlled study on BEV in recurrent glioblastoma with a primary OS endpoint, combination treatment with bevacizumab and lomustine met the prespecified criterion for further investigation in clinical trials, whereas both drugs given as single agent failed to meet this criterion. Clinical trial information: NTR1929.

Abstract: 1

Title: RTOG 0825: Phase III double-blind placebo-controlled trial evaluating bevacizumab (Bev) in patients (Pts) with newly diagnosed glioblastoma (GBM)

Track: Central Nervous System

Authors: Mark R. Gilbert, James Dignam, Minhee Won, Deborah T. Blumenthal, Michael A. Vogelbaum, Kenneth D. Aldape, Howard Colman, Arnab Chakravarti, Robert Jeraj, Terri S. Armstrong, Jeffrey Scott Wefel, Paul D. Brown, Kurt A. Jaeckle, David Schiff, James Norman Atkins, David Brachman, Maria Werner-Wasik, Ritsuko Komaki, Erik P. Sulman, Minesh P. Mehta; University of Texas MD Anderson Cancer Center Department of Neuro-Oncology, Houston, TX; Radiation Therapy Oncology Group, Philadelphia, PA; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Cleveland Clinic Foundation, Cleveland, OH; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; Arthur G. James Cancer Center, The Ohio State University, Columbus, OH; Department of Medical Physics, University of Wisconsin, Madison, WI; University of Texas Health Science Center School of Nursing, Houston, TX; Mayo Clinic, Jacksonville, FL; University of Virginia Medical Center, Charlottesville, VA; National Surgical Adjuvant Breast and Bowel Project and SCCC-CCOP, Goldboro, NC; Arizona Oncology Services Foundation, Phoenix, AZ; Thomas Jefferson University Hospital, Philadelphia, PA; University of Maryland, Baltimore, MD

Background: Chemoradiation (CRT) with temozolomide (TMZ/RT→TMZ) is the standard of care for newly diagnosed GBM. This trial determined if the addition of Bev to standard CRT improves survival (OS) or progression-free survival (PFS) in newly diagnosed GBM. **Methods:** This phase III trial was conducted by the RTOG, NCCTG, and ECOG. Neurologically stable pts > 18 yrs with KPS ≥ 60, and > 1cm^3 tumor tissue block, were randomized to Arm 1: standard CRT + placebo or Arm 2: standard CRT plus Bev (10 mg/kg iv q 2wks). Experimental treatment began at wk 4 of radiation then thru 6-12 cycles of maintenance chemotherapy. Protocol specified co-primary endpoints were OS and PFS, with significance levels of .023 and .002, respectively. At progression, treatment was unblinded and pts allowed to crossover or continue Bev. Symptom, QOL and neurocognitive (NCF) testing was performed in the majority of pts. Secondary analyses evaluated impact of MGMT methylation (meth) and prognostic 9 gene signature status. **Results:** From 978 registered pts, 637 were randomized. Inadequate tissue (n=105) and blood on imaging (n=40) were key reasons for non-randomization. No difference was found between arms for OS (median 16.1 vs. 15.7 mo, p = 0.11). PFS was extended for Arm 2 (7.3 vs. 10.7 mo, p = 0.004). Pts with MGMT meth had superior OS (23.2 vs. 14.3 mo, p < 0.001) and PFS (14.1 vs. 8.2 mo, p < 0.001). Neither the 9 gene signature nor MGMT predicted selective benefit for Bev treatment, but best prognosis pts (MGMT meth, favorable 9-gene), had a worse survival trend with Bev (15.7 vs 25 mo p = 0.08). To date, 128 pts were unblinded on Arm 1 (salvage Bev in 86) and 87 pts on Arm 2 (continued Bev in 39). Increased grade ≥ 3 toxicity was seen with Bev, mostly neutropenia, hypertension, and DVT/PE. **Conclusions:** The addition of Bev for newly diagnosed GBM did not improve OS, did improve PFS but did not reach the significance criterion. MGMT and 9 gene profile did not identify selective benefit, but risk subset results suggested strongly against the upfront use of Bev in the best prognosis pts. Full interpretation of the PFS results incorporating symptom burden, QOL, and NCF is ongoing. Support: NCI U10 CA 21661, U10 CA37422, and Genentech. Clinical trial information: NCT00884741.

Thyroid Cancer

Taefeek Owonikoko, M.D.

NOTES

Abstract: 4

Title: Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial

Track: Plenary Session, Plenary Session Including FDA Commissioner Address, Public Service Award, and Science of Oncology Award and Lecture - Thyroid

Authors: Marcia S. Brose, Christopher Nutting, Barbara Jarzab, Rossella Elisei, Salvatore Siena, Lars Bastholt, Christelle de la Fouchardiere, Furio Pacini, Ralf Paschke, Young Kee Shong, Steven I. Sherman, Johannes WA Smit, John Woojune Chung, Harald Siedentop, Istvan Molnar, Martin Schlumberger; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland; Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; Azienda Ospedaleria Niguarda Ca' Granda, Milano, Italy; Odense University Hospital, Odense, Denmark; Consortium Cancer Thyroïdien, Hospices Civils-Centre Anticancéreux, Lyon, France; Unit of Endocrinology, University of Siena, Siena, Italy; Department for Endocrinology and Nephrology, Leipzig University, Leipzig, Germany; Asan Medicine Center, University of Ulsan College of Medicine, Seoul, South Korea; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; Bayer HealthCare Pharmaceuticals, Montville, NJ; Bayer Pharma AG, Berlin, Germany; Institut Gustave Roussy, Villejuif, France

Background: Sorafenib, an orally active inhibitor of VEGFR1-3 and Raf kinases, has shown promising clinical activity in single-arm phase II studies in radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). The double-blind, randomized, multicenter phase III DECISION trial examined sorafenib efficacy and safety vs placebo in patients with progressive RAI-refractory DTC. **Methods:** Patients with locally advanced/metastatic RAI-refractory DTC who progressed in the preceding 14 months were randomized 1:1 to sorafenib 400 mg bid po or placebo. Placebo patients were allowed to receive sorafenib open-label upon progression. The primary endpoint was progression-free survival (PFS) assessed every 8 wks by independent radiologic review using modified RECIST 1.0 and analyzed by stratified log-rank statistics at $\alpha = 0.01$ (one-sided). Secondary endpoints included overall survival (OS), response rate (RR; complete + partial response [PR]), and safety. **Results:** A total of 417 patients were randomized (207 to sorafenib and 210 to placebo); median age 63 yr, 52% female. Tumor histology by independent assessment was 57% papillary, 25% follicular, and 10% poorly differentiated. 96% of patients had metastatic disease; the most common target lesions were lung (71%), lymph node (40%), and bone (14%). The primary endpoint was met: median PFS 10.8 months (sorafenib) vs 5.8 months (placebo); HR 0.58, 95% CI 0.45–0.75, $p<0.0001$. Median OS has not been reached in either arm; 70% of placebo patients started open-label sorafenib. RR (all PRs) in the sorafenib vs placebo arms was 12.2% and 0.5% ($p<0.0001$) and stable disease ≥ 6 months was 42% and 33%, respectively. The most common any-grade treatment-emergent adverse events in the sorafenib arm included hand–foot skin reaction, diarrhea, alopecia, rash/desquamation, fatigue, weight loss and hypertension. One death in each arm was attributed to study drug. **Conclusions:** Sorafenib significantly improved PFS compared with placebo in patients with progressive RAI-refractory DTC. Tolerability was consistent with the known sorafenib safety profile. Clinical trial information: NCT00895674.

Abstract: 6000

Title: Efficacy of cabozantinib (Cabo) in medullary thyroid cancer (MTC) patients with RAS or *RET* mutations: Results from a phase III study.

Track: Oral Abstract Session, Head and Neck Cancer

Authors: Steven I. Sherman, Ezra E.W. Cohen, Patrick Schoffski, Rossella Elisei, Martin Schlumberger, Lori J. Wirth, Milan Mangeshkar, Dana T. Aftab, Douglas O. Clary, Marcia S. Brose; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Chicago Medical Center, Chicago, IL; University Hospitals Leuven, Department of General Medical Oncology, KU Leuven, Leuven, Belgium; University of Pisa, Pisa, Italy; Institut Gustave Roussy, Villejuit, France; Massachusetts General Hospital, Boston, MA; Exelixis, Inc, South San Francisco, CA; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

Background: Cabo extends progression-free survival (PFS) in patients (pts) with progressive, metastatic MTC (Schöffski, *J Clin Oncol* 30, 2012). Mutations in the *RET* oncogene are associated with most hereditary cases and ~half of sporadic cases of MTC. RAS gene mutations have recently been identified in subsets of *RET* wild type (wt) cases. Therefore, we investigated the association of *RET* (a prospectively defined endpoint) and RAS mutations (a post hoc analysis) with efficacy outcomes in the phase 3 study of cabo in MTC. **Methods:** Pts enrolled into the double-blind, placebo-controlled phase III trial were evaluated for the presence of somatic and germline *RET* mutations using Sanger and next generation methods. A subset of pts determined to be *RET* wt (44 pts) or *RET* unknown (41 pts) were then evaluated for tumor-associated mutations in *KRAS*, *NRAS*, and *HRAS* in codons 12, 13, and 61 by next generation sequencing. Impact of *RET* and RAS gene mutation status was evaluated with respect to PFS and tumor response rate (RR) according to RECIST. **Results:** *RET* status was determined in 65% of the study pts (215/330), of which 79% harbored an activating mutation, and 21% were *RET* wt. All *RET* mutational subgroups (*RET* mutated, *RET* wt, and *RET* unknown) showed hazard ratios indicating PFS benefit from cabo treatment, and demonstrated RRs between 22% and 32%. However pts harboring a *RET* mutation had longer median PFS on cabo (60 wks) than pts with wt RET (25 wks, PFS difference p=0.0001). Also, pts with the poor prognosis mutation *RET* M918T showed a longer median PFS on cabo treatment (61 wks) than pts with any other *RET* mutation (36 wks, PFS difference p=0.009). Patients with hereditary MTC had similar PFS to those with sporadic disease, and the presence of the common *RET* polymorphism G691S had no effect on either PFS or RR. Sixteen of 85 tested pts (5% of total study pts) with wt or unknown *RET* status were found to harbor a RAS gene mutation. The RAS-mutated pts showed a similar RR (31%) and PFS (47 wks) as *RET* mutated pts (32% and 60 wks). **Conclusions:** While hazard ratios indicate PFS improvement for all *RET* subgroups on cabo, the extent of benefit may depend in part on *RET* genotype. Cabo treatment benefit is also seen in pts harboring a RAS mutation. Clinical trial information: NCT00704730.

Abstract: 6025

Title: Re-differentiation of radioiodine-refractory *BRAF* V600E-mutant thyroid carcinoma with dabrafenib: A pilot study.

Track: Poster Discussion Session, Head and Neck Cancer

Authors: Stephen M. Rothenberg, David G McFadden, Edwin Palmer, Gilbert H Daniels, Lori J. Wirth; Massachusetts General Hospital Cancer Center, Boston, MA; Massachusetts General Hospital Thyroid Unit, Boston, MA; Massachusetts General Hospital Department of Radiology, Boston, MA; Massachusetts General Hospital, Boston, MA

Background: Resistance to radioactive iodine is a leading cause of mortality in differentiated thyroid carcinoma. The MAPK pathway is a major determinant of iodine uptake into thyroid carcinoma cells. Mutations in BRAF activate this pathway, resulting in resistance to radioactive iodine. A pilot study using the MEK1/2 inhibitor, selumetinib, (Ho, ASCO 2012) increased radioiodine uptake in a subset of thyroid cancers. **Methods:** This is a single institution, single arm pilot study investigating the potential for the BRAF inhibitor dabrafenib to induce radioiodine uptake in metastatic, BRAF-mutant, radioiodine-refractory papillary thyroid carcinoma (PTC). The primary endpoint is increased radioiodine uptake demonstrated on a 4mCi 131-I whole body scan. Patients with increased uptake receive 14 additional days of dabrafenib followed by treatment with 150mCi 131-I. Secondary endpoints include safety and tolerability and clinical benefit as measured by decreases in serum thyroglobulin and objective response rate per modified RESIST 1.1. **Results:** To date, 7 patients have been enrolled. All had negative 131-I scans within 14 months of enrollment. No dose adjustments for toxicity have been needed. One patient developed reversible hypophosphatemia and a second developed a benign skin lesion. 3 of 5 evaluable patients developed radioiodine uptake after 28 days of dabrafenib, and new radioiodine-avid lesions were demonstrated in all three after receiving a therapeutic dose of 131-I. All three patients demonstrated increases in thyroglobulin levels during treatment with dabrafenib. **Conclusions:** This initial data suggests that a subset of patients with radioiodine-resistant BRAF-mutant PTC demonstrate new iodine uptake following treatment with dabrafenib. Reuptake may correlate with increases in thyroglobulin, suggestive of re-differentiation. It is not yet known whether increased uptake of radioactive iodine will translate into a radiographic response. Two patients failed to convert to radioiodine-sensitive disease; it is possible that BRAF inhibition was incomplete in these patients and/or determinants other than BRAF mutation status contribute to radioiodine sensitivity. Clinical trial information: NCT01534897.

Abstract: 6024

Title: Phase II study of everolimus and sorafenib for the treatment of metastatic thyroid cancer.

Track: Poster Discussion Session, Head and Neck Cancer

Authors: Eric Jeffrey Sherman, Alan Loh Ho, Matthew G. Fury, Shrujal S. Baxi, Sofia Haque, Brynna Lane Lipson, Sarah Kurz, James A. Fagin, David G. Pfister; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Everolimus is an oral inhibitor of the mammalian target of rapamycin (mTOR). Unpublished work from the Fagin lab shows that mTORC1 is also required for the growth promoting effects of the oncoproteins RET/PTC, RAS and BRAF in rat thyroid PCCL3 cells. Further work shows synergy of mTORC inhibitors with RET kinase inhibitors in medullary thyroid cancer cell lines. Sorafenib is an oral kinase inhibitor with in vitro activity against multiple targets, including RAF, RET, VEGFR1, and VEGFR2 that is compendium approved for the treatment of radioactive iodine-refractory (RAIR) and medullary (MTC) thyroid cancer. **Methods:** The study was a single institution, two-stage phase II design. Primary objective was response rate initiated on 9/21/2010. Eligible patients (pts) had progressive, RAIR/fluorodeoxyglucose (18-F)-avid, recurrent/metastatic, non-anaplastic, thyroid cancer; RECIST measurable disease; and adequate organ/marrow function. Sorafenib was given at 400 mg orally twice a day and Everolimus at 5 mg orally once daily. 41 patients were enrolled; 36 were eligible for the primary endpoint of response and 3 were evaluable for toxicity only at the data cutoff date of 1/10/13. Seventeen patients are still actively on study. Mutational analyses of tissue is ongoing. **Results:** Of the 41 eligible pts, demographics: female-44% (18); median age-61 years (35-79). Grade 4-5 adverse events at least possibly related to drug: grade 4- Alanine Aminotransferase Increase (1 pt): grade 4- Hyperglycemia (1 pt): grade 4-Pancreatitis (1 pt). Histology and response data by partial response, confirmed and unconfirmed, (PR), stable disease (SD) and progression of disease (POD) are in the table below. The median time on treatment is 167 days (range 1 to 797 days) at the cutoff date of 1/10/2013. **Conclusions:** The combination of sorafenib and everolimus shows promising results, especially in the Hurthle cell and medullary subgroups where data from studies at Ohio State have suggested very poor response to sorafenib alone. Clinical trial information: NCT01141309.

Abstract: 6023

Title: A phase II study of everolimus in patients with aggressive RAI refractory (RAIR) thyroid cancer (TC).

Track: Poster Discussion Session, Head and Neck Cancer

Authors: Jochen H. Lorch, Naifa Busaidy, Daniel T Ruan, Pasi A. Janne, Sewanti Atul Limaye, Lori J. Wirth, Justine A. Barletta, Guilherme Rabinowits, Levi A. Garraway, Eliezer Mendel Van Allen, Nikhil Wagle, Glenn J. Hanna, Krzysztof Misiukiewicz, Margaret Suda, Tyler C Haddad, Catherine E Devine, Amy Williams, Ghulam Warsi, Marshall R. Posner, Robert I. Haddad; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Massachusetts General Hospital, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Department of Medicine, Hematology/Oncology, Mount Sinai Medical Center, New York, NY; Medical Oncology, Dana Farber Cancer Institute, Boston, MA; Novartis, East Hanover, NJ; Novartis Pharmaceuticals, East Hanover, NJ; Mount Sinai Medical Center, New York, NY

Background: We present results of an open label phase II study of the mTOR inhibitor Everolimus in patients (pts) with RAIR TC. **Methods:** Pts with metastatic, incurable RAIR TC who had shown radiographic progression within 6 months prior to enrollment received Everolimus 10mg orally once daily. Responses were monitored by CT's every two months. The primary endpoint was progression free survival. Sequential biopsies were obtained in selected pts. **Results:** Enrollment to the differentiated TC (DTC) cohort finished in Jan 2013 and included 33 pts, among them 11 with Hurthle cell TC. Exploratory cohorts enrolled 10 pts with medullary [MTC] and 5 with anaplastic [ATC] with 2 added openings remaining for ATC. For the DTC cohort, median time on study to date is 10 months (mo) (<1-23+). 31 pts are evaluable at this time. PFS in the DTC cohort by Kaplan-Meier (K-M) analysis is 16.0 mo (95%CI 10-NR). Currently, disease stability for 6 and 12 mo or more was achieved in 18 and 10/31 pts, respectively, 11 pts remain on study. Median OS was not reached but 1 year survival by K-M analysis was 76%. One pt achieved a PR. 3 pts with DTC underwent sequential biopsies which revealed activation of autophagy while markers for apoptosis were not detected. Among 10 MTC pts, one achieved a PR and 9 pts had stable disease for 6 mo or more (6-33+). Among 5 ATC pts, 3 progressed, one has ongoing disease stability for 5 mo. One patient achieved a complete response that lasted for 18 mo and whole exome sequencing revealed somatic loss of function mutation affecting the Tuberous Sclerosis 2 (TSC2) protein, a negative regulator of mTOR activity [TSC2 (Q1178*) and FLCN (R17fs)]. Most common treatment-related adverse events were as anticipated and included fatigue, stomatitis and infections. Grade (gr) 3 events included infection 5, weight loss 3, leukopenia 3, thrombocytopenia 3, fatigue 3, hypophosphatemia 2, stomatitis 2, pneumonitis 1 and thrombosis 1pts. One pt had gr 4 hypercholesterinemia and one pt had gr 4 leukopenia. **Conclusions:** Everolimus has significant anti-tumor activity in pts with advanced TC. Activation of autophagy could account for high rate of disease stability. Sequencing may identify mechanistic basis and predictive markers for treatment response. Clinical trial information: NCT00936858.

Melanoma

David H. Lawson, M.D.

NOTES

Abstract: 9009

Title: Clinical efficacy and safety of lambrolizumab (MK-3475, Anti-PD-1 monoclonal antibody) in patients with advanced melanoma.

Track: Oral Abstract Session, Melanoma/Skin Cancers

Authors: Antoni Ribas, Caroline Robert, Adil Daud, F. Stephen Hodi, Jedd D. Wolchok, Richard Kefford, Amita Patnaik, Wen-Jen Hwu, Jeffrey S. Weber, Anthony Joshua, Peter Hersey, Tara C. Gangadhar, Richard Wayne Joseph, Roxana Stefania Dronca, Hassane M. Zarour, Scot Ebbinghaus, Kevin Gergich, Xiaoyun (Nicole) Li, Soonmo Peter Kang, Omid Hamid; Med-Hematology & Oncology, University of California, Los Angeles, Los Angeles, CA; Institut Gustave Roussy, Villejuif, France; University of California, San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; Westmead Hospital and Melanoma Institute Australia, University of Sydney, Sydney, Australia; START Center for Cancer Care, San Antonio, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; Princess Margaret Cancer Center, Toronto, ON, Canada; Calvary Mater Newcastle, Waratah, Australia; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Mayo Clinic Cancer Center, Jacksonville, FL; Mayo Clinic, Department of Medical Oncology, Rochester, MN; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Merck & Co, Inc, North Wales, PA; Merck & Co, Inc, Rahway, NJ; The Angeles Clinic and Research Institute, Los Angeles, CA

Background: Programmed death-1 (PD-1) is an inhibitory T-cell co-receptor that may lead to suppression of antitumor immunity. Lambrolizumab is a humanized monoclonal IgG4 antibody against PD-1. This study explored the safety and clinical activity of lambrolizumab in patients (pts) with advanced melanoma (MEL). **Methods:** In this ongoing phase 1b expansion study of MEL pts with or without previous ipilimumab (IPI) treatment, lambrolizumab was administered IV every 2 or 3 weeks until disease progression or unacceptable toxicity. Tumor response was assessed every 12 weeks by independent, central, blinded radiographic review per immune-related response criteria and RECIST 1.1. **Results:** As of December 1, 2012, 294 pts with MEL were enrolled, including 179 IPI-naive and 115 IPI-pretreated. Pts received lambrolizumab 10 mg/kg (n = 183) or 2 mg/kg (n = 111). Preliminary data from the first 85 consecutive pts dosed before April 25, 2012, who had independent radiologic review available as of December 3, 2012, indicate a confirmed overall response rate per RECIST 1.1 of greater than 35%, pooled across all doses and schedules and including both IPI-naive and IPI-pretreated patients. The median duration of response has not been reached as only 2 pts who had initial response discontinued due to disease progression, but the duration of confirmed responses range from 28+ to 240+ days (up to 8+ months). Among 133 pts who were dosed with lambrolizumab before July 31, 2012, and evaluable for adverse events (AEs) as of September 28, 2012, fatigue (22%), rash (18%), and pruritus (14%) were the most common drug-related AEs (mostly grade 1/2). The incidence of drug-related grade 3/4 AEs was 10% (24% regardless of attribution). Four drug-related cases of pneumonitis were reported, all of grade 1/2. Grade 3/4 drug-related hypothyroidism (n = 1) and hyperthyroidism (n = 1) were noted. **Conclusions:** Preliminary data suggest that lambrolizumab has significant antitumor activity and is well tolerated with manageable side effects in both IPI-naive and IPI-pretreated MEL pts. These data have led to an ongoing, international, randomized study of lambrolizumab versus chemotherapy in IPI-pretreated MEL. Clinical trial information: NCT01295827.

Clinical Efficacy and Safety of Lambrolizumab (MK-3475, Anti-PD-1 Monoclonal Antibody) in Patients With Advanced Melanoma

Antoni Ribas,[1] Caroline Robert,[2] Adil Daud,[3] F. Stephen Hodi,[4] Jedd Wolchok,[5] Richard Kefford,[6] Amita Patnaik,[7] Wen-Jen Hwu,[8] Jeffrey Weber,[9] Anthony Joshua,[10] Peter Hersey,[11] Tara C. Gangadhar,[12] Richard Joseph,[13] Roxana Dronca,[14] Hassane Zarour,[15] Scot Ebbinghaus,[16] Kevin Gergich,[16] Xiaoyun Li,[16] S. Peter Kang,[17] Omid Hamid[18]

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Drug-Related Adverse Events

Observed in >5% of Patients (N = 135)

Adverse Event	All Grades, n (%)	Grade 3-4, n (%)
Any	107 (79.3)	17 (12.6)
Fatigue	41 (30.4)	2 (1.5)
Rash	28 (20.7)	3 (2.2)
Pruritus	28 (20.7)	1 (0.7)
Diarrhea	27 (20.0)	1 (0.7)
Myalgia	16 (11.9)	0
Headache	14 (10.4)	0
Increased AST	13 (9.6)	2 (1.5)
Asthenia	13 (9.6)	0
Nausea	13 (9.6)	0
Vitiligo	12 (8.9)	0
Hypothyroidism	11 (8.1)	1 (0.7)
Increased ALT	11 (8.1)	0
Cough	11 (8.1)	0
Pyrexia	10 (7.4)	0
Chills	9 (6.7)	0
Abdominal pain	7 (5.2)	1 (0.7)

Presented by: Antoni Ribas

Safety Profile by Dose

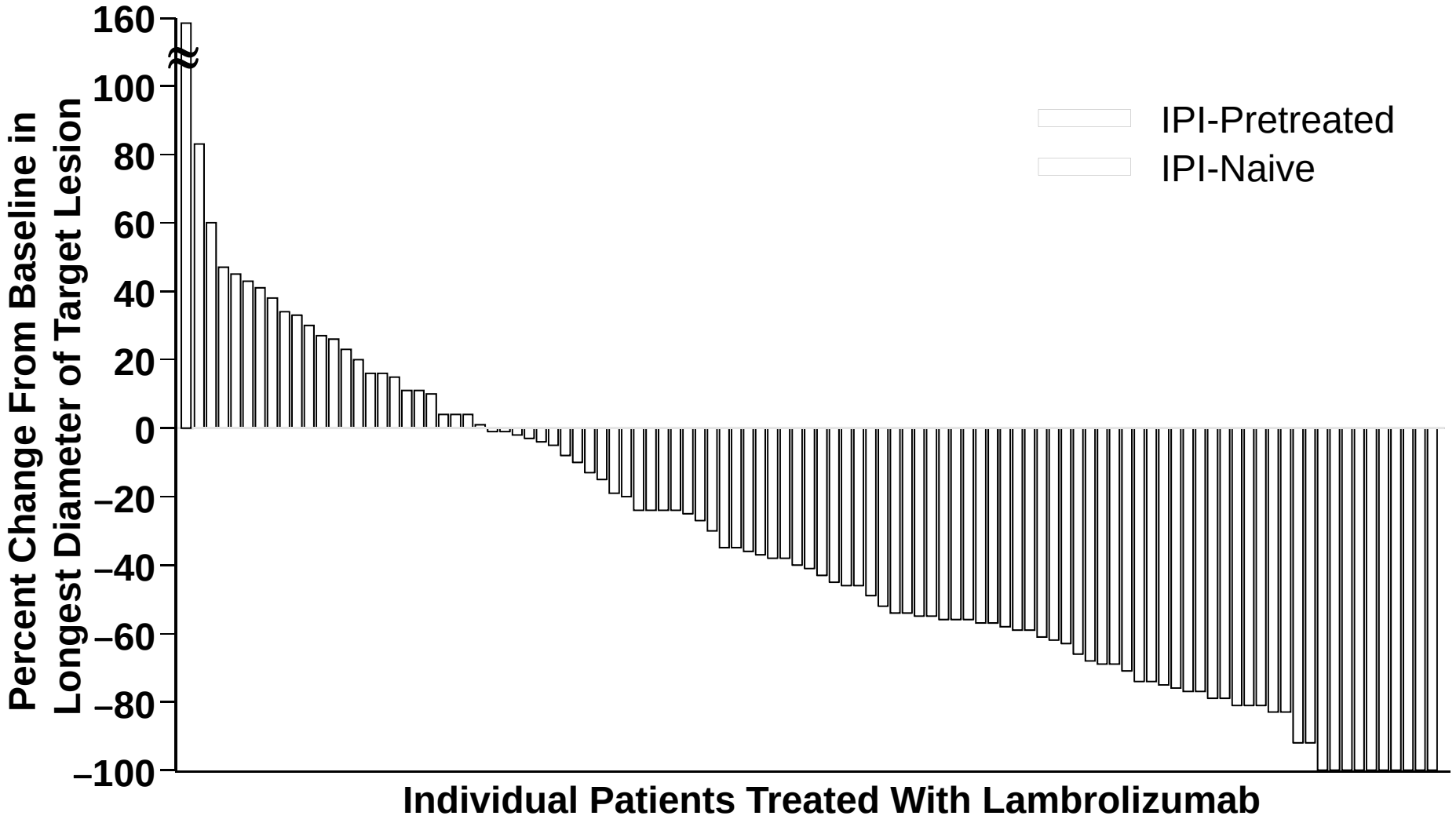
	10 mg/kg Q2W n = 57	10 mg/kg Q3W n = 56	2 mg/kg Q3W n = 22	Total N = 135
Any grade treatment-related adverse events	91%	73%	64%	79%
Grade 3-4 treatment-related adverse events	23%	4%	9%	13%
Time on therapy, median (range), wk	40.1 (1.0–53.3+)	20.6 (1.0–48.1+)	18.1 (1.0–39.1+)	23.1 (1.0–53.3+)
Number of doses, median (range)	12 (1–26+)	6.5 (1–18+)	7 (1–14+)	8 (1–26+)

Presented by: Antoni Ribas

AEs of Inflammatory or Immune Nature

- Pneumonitis (grade 1-2) in 6 patients (4.4%)
- Hypothyroidism in 11 patients (8.1%)
  - One case of grade 3 hyperthyroidism + grade 2 adrenal insufficiency
- Transaminase elevations (grade 3-4) in 2 patients (1.5%)
- Renal insufficiency (grade 3) in 2 patients (1.5%)
- 1 patient death during study participation
  - 96-year-old man with suspected grade 2 pneumonitis; found to have pneumonia and died after complications from bronchoscopy and biopsies
- Most treatment-related AEs successfully managed with treatment discontinuation, supportive care, and, occasionally, glucocorticoids

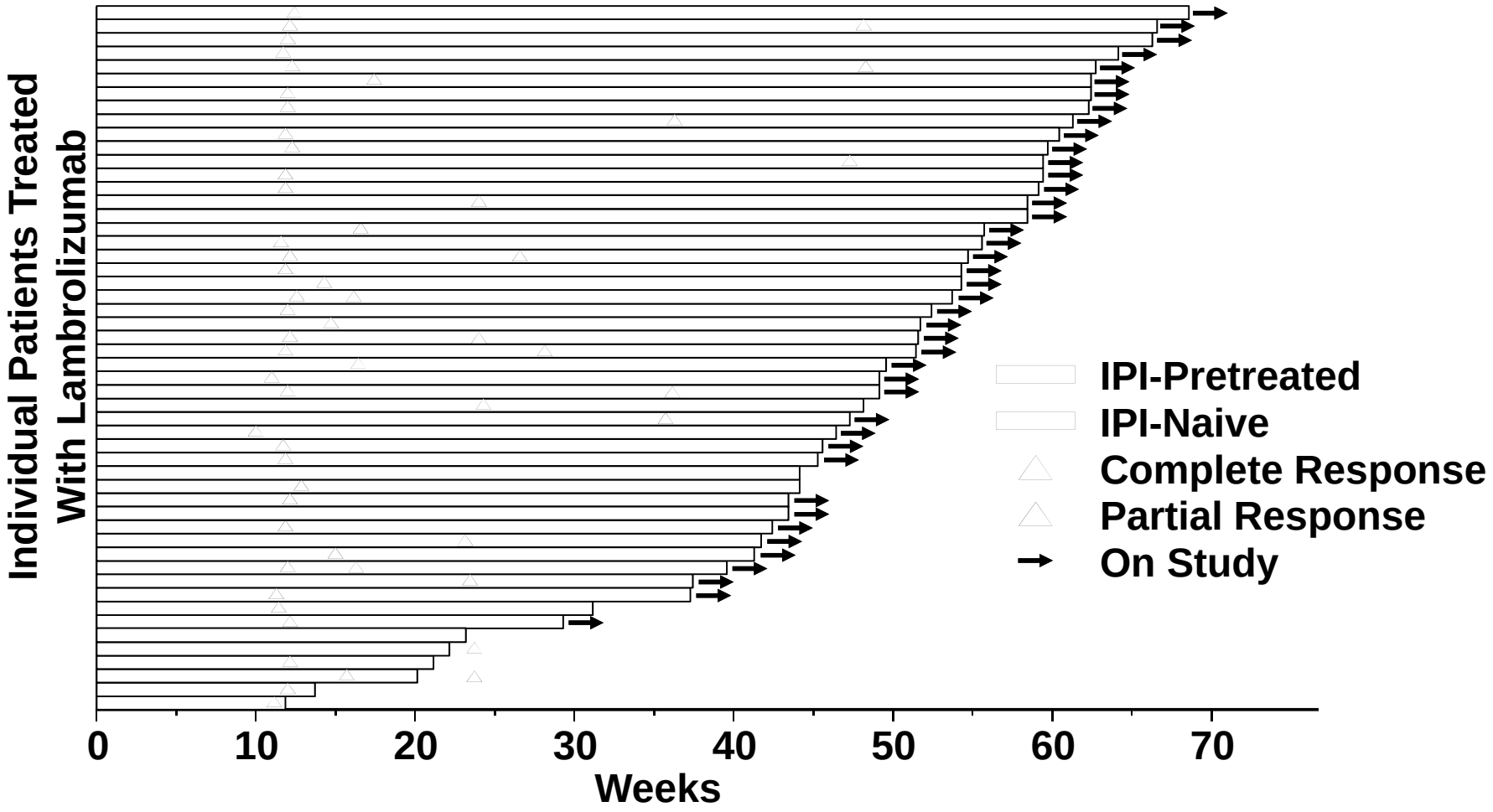
Part B: Maximum Change From Baseline in Tumor Size (Independent Central Review per RECIST 1.1)



Presented by: Antoni Ribas

Time to Response and On-Study Duration

(Independent Central Review per RECIST 1.1)



The median duration of response had not been reached at the time of analysis, with median follow-up time of 11 months.

Presented by: Antoni Ribas

Confirmed Objective Response Rate (ORR) by Dosing Regimen and Prior Ipilimumab Treatment

Lambrolizumab Dose	Prior IPI Treatment	RECIST 1.1, Independent Central Review			irRC, Investigator Assessment	
		N	ORR, % (95% CI)	Response Duration Range, mo	N	ORR, % (95% CI)
Total		117	38 (25–44)*	1.9+ – 10.8+	135	37 (29–45)
10 mg/kg Q2W	Naive	39	49 (32–65)	1.9+ – 10.8+	41	56 (40–72)
	Treated	13	62 (32–86)	2.8+ – 8.3+	16	56 (30–80)
	Total	52	52 (38–66)	1.9+ – 10.8+	57	56 (42–69)
10 mg/kg Q3W	Naive	19	26 (9–51)	2.6 – 5.6+	24	33 (16–55)
	Treated	26	27 (12–48)	2.8+ – 8.3+	32	22 (9–40)
	Total	45	27 (15–42)	2.6 – 8.3+	56	27 (16–40)
2 mg/kg Q3W	Naive	20	25 (9–49)	2.1+ – 5.5+	22	14 (3–35)

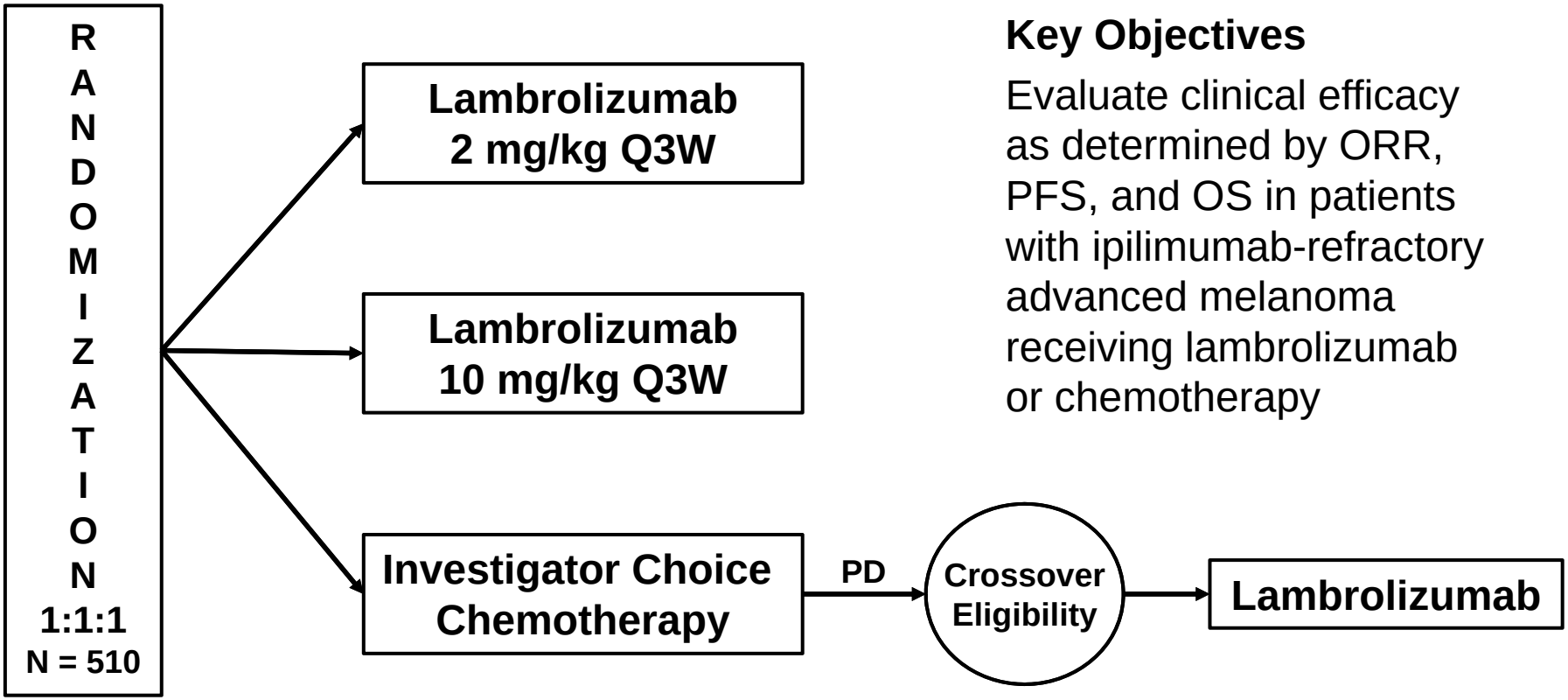
***Including unconfirmed responses, ORR was 44% across all doses and 56% for 10 mg/kg Q2W, 36% for 10 mg/kg Q3W, and 35% for 2 mg/kg Q3W.**
"+" indicates censored observation.

Presented by: Antoni Ribas

Summary

- Confirmed response rate per RECIST 1.1 of 38%
  - 52% ORR, including 10% complete response rate, at 10 mg/kg Q2W
  - 42 of 52 (80%) responders are on study at the time of analysis
- Acceptable, manageable toxicity profile
  - Highest rate of drug-related AEs at 10 mg/kg Q2W
- Efficacy and safety similar in ipilimumab-naive and -treated patients
- Clinical development of lambrolizumab is ongoing in melanoma, NSCLC, breast cancer, head and neck cancer, and bladder cancer

Global, Phase II Study of Lambrolizumab vs Chemotherapy for Ipilimumab-Refractory Advanced Melanoma (NCT01704287)

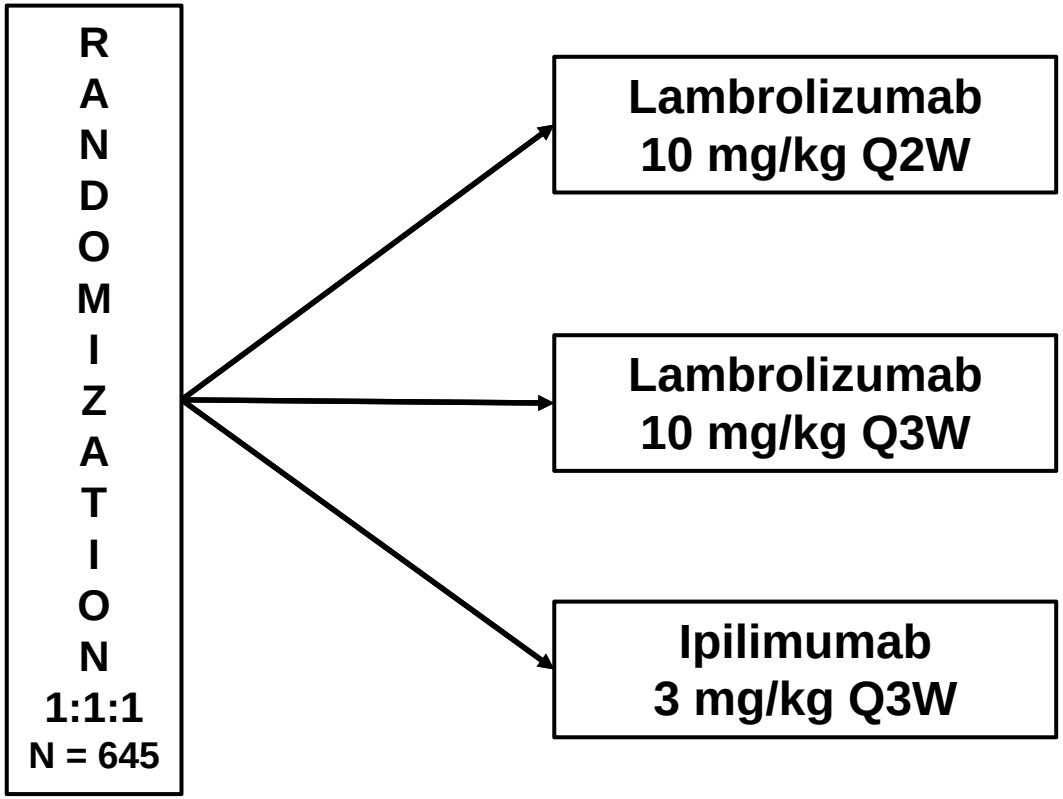


Key Objectives

Evaluate clinical efficacy as determined by ORR, PFS, and OS in patients with ipilimumab-refractory advanced melanoma receiving lambrolizumab or chemotherapy

Presented by: Antoni Ribas

Global, Phase III Study of Lambrolizumab vs Ipilimumab as First- or Second-Line Therapy for Advanced Melanoma (NCT01866319)



Key Objective

Evaluate clinical efficacy as determined by ORR, PFS, and OS in patients with ipilimumab-naive advanced melanoma receiving lambrolizumab or ipilimumab as first- or second-line therapy

Presented by: Antoni Ribas

Abstract: 9010

Title: Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic melanoma (mM).

Track: Oral Abstract Session, Melanoma/Skin Cancers

Authors: Omid Hamid, Jeffrey Alan Sosman, Donald P. Lawrence, Ryan J. Sullivan, Nageatte Ibrahim, Harriet M. Kluger, Peter D. Boasberg, Keith Flaherty, Patrick Hwu, Marcus Ballinger, Ahmad Mokatrin, Marcin Kowanetz, Daniel S. Chen, F. Stephen Hodi; The Angeles Clinic and Research Institute, Los Angeles, CA; Vanderbilt-Ingram Cancer Center, Nashville, TN; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Yale University, New Haven, CT; The Angeles Clinic and Research Institute, Santa Monica, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Genentech, Inc., South San Francisco, CA; Genentech Inc., South San Francisco, CA

Background: mM is an immunotherapy responsive disease where PD-L1 overexpression is prevalent. MPDL3280A, a human monoclonal antibody containing an engineered Fc-domain designed to optimize efficacy and safety, targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. Initial antitumor activity observed during dose escalation supported further expansion in mM with MPDL3280A as monotherapy and in combination with targeted therapy. **Methods:** Pts with mM of any histologic subtype received MPDL3280A administered IV q3w for up to 1 y. Objective response rate (ORR) was assessed by RECIST v1.1. Reported ORR includes u/cCR and u/cPR. In addition, a separate Ph 1b was initiated to evaluate the safety and efficacy of MPDL3280A with vemurafenib (vem) in pts with *BRAF*-V600 mutated mM. **Results:** As of Jan 10, 2013, 45 mM pts were treated at ≤1 (n=4), 10 (n=10), 25 (n=20) and 20 mg/kg (n=11) and evaluable for safety. Median pt age was 63 y (range 21-83 y), 100% were PS 0-1, 91% had prior surgery and 64% received prior systemic therapy. Pts received MPDL3280A treatment for a median duration of 127 days (range 1-282). The incidence of all G3/4 AEs, regardless of attribution, was 33%, including hyperglycemia (7%), elevated ALT (7%) and elevated AST (4%). No G3-5 pneumonitis was reported. No treatment-related deaths occurred on study. 35 mM pts who initiated treatment at doses of 1-20 mg/kg and enrolled prior to Jul 1, 2012, were evaluable for efficacy. An ORR of 26% (9/35) was observed, with all RECIST responses ongoing or improving. Further, some responding pts experienced tumor shrinkage within days of initial treatment. The 24-week PFS was 35%. Several additional pts had delayed antitumor activity after apparent radiographic progression and were counted as PD for the above analyses. Analysis of mandatory archival tumors showed a correlation between PD-L1 status and efficacy. Further, of three initial pts treated with MPDL3280A and vem, 2 experienced tumor shrinkage, including 1 CR. **Conclusions:** MPDL3280A was well tolerated as monotherapy, and durable ORs were observed. Therefore, further assessment of MPDL3280A as monotherapy and combination therapy is warranted. Clinical trial information: NCT01375842.

Clinical Activity, Safety and Biomarkers of MPDL3280A, an Engineered PD-L1 Antibody in Patients With Metastatic Melanoma

Omid Hamid,[1] Jeff Sosman,[2] Donald Lawrence,[3] Ryan J Sullivan,[3] Nageatte Ibrahim,[4] Harriet Kluger,[5] Peter Boasberg,[1] Keith Flaherty,[3] Patrick Hwu,[6] Marcus Ballinger,[7] Ahmad Mokatrin,[7] Marcin Kowanetz,[7] Daniel S. Chen[7] and F. Stephen Hodi[4]

[1]*The Angeles Clinic and Research Institute,* [2]*Vanderbilt-Ingram Cancer Center,* [3]*Massachusetts General Hospital,* [4]*Dana-Farber Cancer Institute,* [5]*Yale University,* [6]*MD Anderson,* [7]*Genentech Inc.*

MPDL3280A Phase Ia in Melanoma: Safety Overview

- No treatment-related deaths
- No maximum tolerated dose or dose-limiting toxicities
- The majority of adverse events (AEs) were transient Grade 1-2 and did not require intervention

Most Common AEs of Any Grade, Regardless of Attribution	Total, n (%) N = 44	
	Any Grade	Grade 3-4
Fatigue	26 (59%)	1 (2%)
Headache	14 (32%)	0
Diarrhea	13 (30%)	1 (2%)
Pruritus	11 (25%)	0
Dyspnea	10 (23%)	0
Nausea	10 (23%)	0
Constipation	9 (21%)	0
Pyrexia	9 (21%)	0
Decreased appetite	9 (21%)	0
Cough	9 (21%)	0
Arthralgia	7 (16%)	1 (2%)
AST increased	7 (16%)	2 (5%)
Chills	7 (16%)	0
Insomnia	7 (16%)	0
Rash	7 (16%)	0

Data cutoff Feb 1, 2013. Table includes AEs occurring in > 15% of patients.

MPDL3280A Phase Ia in Melanoma: Grade 3-4 AEs

- **No pneumonitis or colitis observed**
- **Immune-related* Grade 3-4 AEs, n = 2† patients (5%)**
- **Treatment-related* Grade 3-4 AEs, n = 6 patients (14%)**

Most Common Grade 3-4 AEs, Regardless of Attribution	All Dose Cohorts N = 44; n (%)
All Grade 3-4	**16 (36%)**
Hyperglycemia	4 (9%)
Increased ALT	3 (7%)
Increased AST	2 (5%)
Back pain	2 (5%)

Data cutoff Feb 1, 2013, Grade 3-4 AEs occurring in ≥ 2 patients.
*Investigator-assessed.
†Events included increased AST and/or ALT; 1 event led to discontinuation of MPDL3280A treatment.

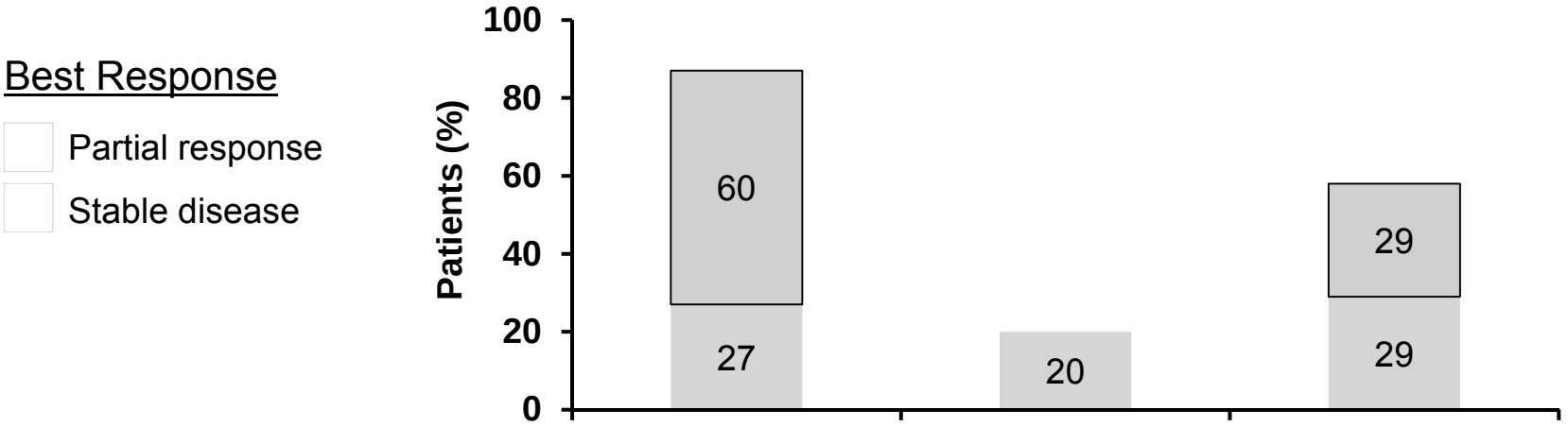
MPDL3280A Phase Ia: Efficacy Summary
Investigator Assessed

	ORR*	SD of 24 Weeks or Longer	24-Week PFS
Overall population (N = 140)	21%	16%	45%
Melanoma (n = 38)	**29%**	**5%**	**43%**
Cutaneous† (n = 27)	33%	7%	54%
Mucosal† (n = 4)	25%	0	25%
Ocular† (n = 4)	0	0	0

* ORR includes unconfirmed PR/CR and confirmed PR/CR.
† 3 patients had undetermined histology status.
Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.
7 overall population patients and 1 melanoma patient who did not have a post-baseline scan were included as non-responders.

MPDL3280A Phase Ia: Summary of Response by PD-L1 IHC Status

Investigator-Assessed Best Overall Response Rate (ORR), n/n (%)			
	PD-L1 Positive	**PD-L1 Negative**	**All†**
Overall population ORR (N = 140)	13/36 (36%)	9/67 (13%)	29/140 (21%)
Melanoma ORR (N = 38)	**4/15 (27%)**	**3/15 (20%)**	**11/38 (29%)**
Melanoma PR + SD (N = 38), %	**87%**	**20%**	**58%**



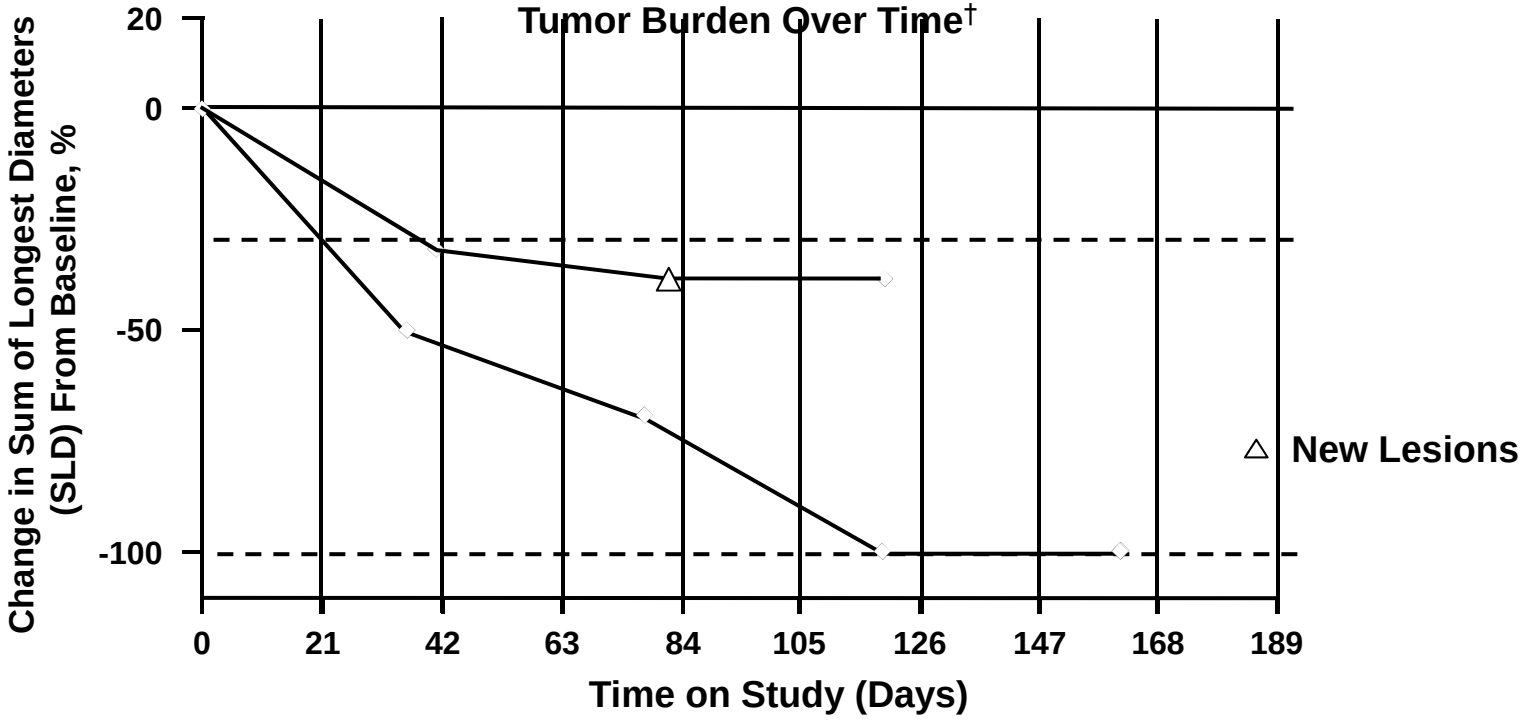
* ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1.
† All patients include PD-L1–positive, PD-L1–negative and patients with unknown tumor PD-L1 status.
Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.

MPDL3280A + Vemurafenib Initial Safety and Efficacy

Cohort 1: MPDL3280A 20 mg/kg q3w + 720 mg vemurafenib BID (N = 3; melanoma)

AE Summary:

- Rash (Grade 3) and flu-like symptoms (Grade 1-2)* observed in cycle 1
- AST/ALT elevation (up to Grade 3) observed in cycles 1-4
- Resolved with vemurafenib interruption and reduction



Currently evaluating staggered initiation of MPDL3280A

* Included fever, headache, sore throat, arthralgia, chills, fatigue.

† 1 patient with PD at 8 weeks was unevaluable for target lesion change.

Conclusions

- MPDL3280A generally well tolerated in metastatic melanoma
  - No pneumonitis or colitis observed
  - No dose-limiting toxicities up to 20 mg/kg (highest dose tested)
- 29% ORR with responses continuing in 10/11 responders
  - Responses can be rapid or delayed
- Patients with PD-L1–positive tumor tissue had a higher rate of disease control as defined by ORR and SD
- Vemurafenib combination study ongoing:
  - Consistent toxicities observed; majority non-recurrent post-cycle 1
  - CR experienced by 1 of first 3 patients

Combinations

Abstracts 9012, 9011, and CRA9007

Abstract: 9012

Title: Safety and clinical activity of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients (pts) with advanced melanoma (MEL).

Track: Clinical Science Symposium, PD1/PDL1: An Effective Target in Melanoma

Authors: Jedd D. Wolchok, Harriet M. Kluger, Margaret K. Callahan, Michael Andrew Postow, Ruth Ann Gordon, Neil Howard Segal, Naiyer A. Rizvi, Alexander M. Lesokhin, Kathleen Reed, Matthew M. Burke, Anne Caldwell, Stephanie Anne Kronenberg, Blessing Agunwamba, William Feely, Quan Hong, Christine E. Horak, Alan J. Korman, Jon M. Wigginton, Ashok Kumar Gupta, Mario Sznol; Memorial Sloan-Kettering Cancer Center, New York, NY; Yale School of Medicine; Yale Cancer Center, New Haven, CT; Memorial-Sloan Kettering Cancer Center, New York, NY; Bristol-Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Redwood City, CA

Background: CTLA-4 and PD-1 are critical immune checkpoint receptors. In MEL pts, ipilimumab (anti-CTLA-4) prolonged survival in two phase III trials, and nivolumab (anti-PD-1) produced an objective response rate (ORR) of 31% (n=106) in a phase I trial. PD-1 is induced by CTLA-4 blockade, and combined blockade of CTLA-4/PD-1 showed enhanced antitumor activity in murine models. Thus, we initiated the first phase 1 study to evaluate nivolumab/ipilimumab combination therapy. Methods: MEL pts with ≤3 prior therapies received IV nivolumab and ipilimumab concurrently, q3 wk × 4 doses, followed by nivolumab alone q3 wk × 4 (Table). At wk 24, combined treatment was continued q12 wk × 8 in pts with disease control and no DLT. In two sequenced-regimen cohorts, pts with prior standard ipilimumab therapy were treated with nivolumab (q2 wk × 48). Results: As of Dec. 6, 2012, 69 pts were treated. We report efficacy data on 37 pts with concurrent therapy in completed cohorts 1-3 (Table); ORR was 38% (95% CI: 23-55). In cohort 2 (MTD), ORR was 47% and 41% of pts had ≥80% tumor reduction at 12 wk (Table) with some pts showing rapid responses, prompt symptom resolution, and durable CRs. Related adverse events (rAEs) for concurrent therapy were similar in nature with some higher in frequency than those typically seen for the monotherapies and were generally manageable using immunosuppressants. Cohort 3 exceeded the MTD (DLT: gr 3-4 ↑ lipase). At the MTD, gr 3-4 rAEs occurred in 59% of pts and included uveitis/choroiditis, colitis, and reversible lab abnormalities. Conclusions: Nivolumab and ipilimumab can be combined with a manageable safety profile. Clinical activity for concurrent therapy appears to exceed that of published monotherapy data, with rapid and deep tumor responses (≥80% tumor reduction at 12 wk) in 30% (11/37) of pts. A phase III trial is planned to compare concurrent combination dosing with each monotherapy. Clinical trial information: NCT01024231.

Clinical activity and safety of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients with advanced melanoma

Jedd D. Wolchok,[1] Harriet Kluger,[2] Margaret K. Callahan,[1] Michael A. Postow,[1] RuthAnn Gordon,[1] Neil H. Segal,[1] Naiyer A. Rizvi,[1] Alexander M. Lesokhin,[1] Kathleen Reed,[2] Matthew M. Burke,[2] Anne Caldwell,[2] Stephanie A. Kronenberg,[1] Blessing U. Agunwamba,[1] William Feely,[3] Quan Hong,[3] Christine E. Horak,[3] Alan J. Korman,[4] Jon M. Wigginton,[3] Ashok Gupta,[3] and Mario Sznol[2]

[1]Ludwig Center at Memorial Sloan-Kettering Cancer Center, New York, NY;
[2]Yale University School of Medicine and Yale Cancer Center, New Haven, CT;
Bristol-Myers Squibb, [3]Princeton, NJ and [4]Redwood City, CA

Ipilimumab and Nivolumab Clinical Experience in Patients with Advanced Melanoma

- **Ipilimumab:** 3 mg/kg every 3 wk, 4 doses (Phase 3)
  - ORR: 11%; 2 patients with CR[1]
  - Median OS: 10.1 mo;[1] 4-year survival rate (Phase 2 studies): 18%[2]
  - Grade 3-4 related AEs: 23%; included diarrhea (5%) and colitis (5%)[1]

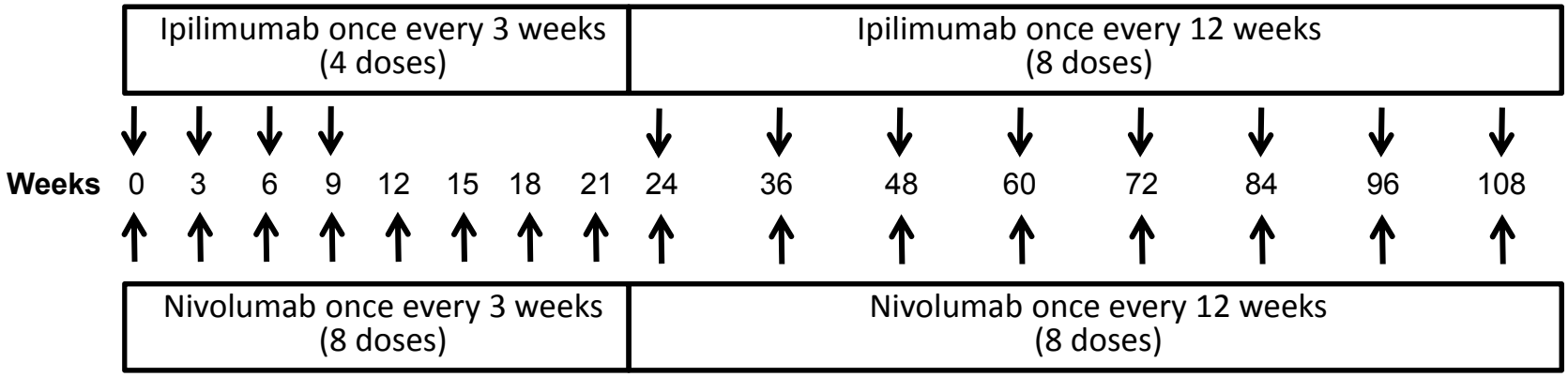
- **Nivolumab**: 0.1 mg/kg to 10 mg/kg every 2 wk, ≤48 doses (Phase 1b)
  - ORR: 41%; 1 patient with CR (3 mg/kg)[3]
  - Median OS: 16.8 mo;[4] 2-year survival rate: 43%[4]
  - Grade 3-4 related AEs: 14%; included diarrhea (1%), pneumonitis (1%), and hypophosphatemia (1%)[3]

[1]Hodi et al. NEngl J Med. 2010;363:711-23. [2]Wolchok et al. Ann Oncol 2013 May10 [Epub ahead of print].
[3]Topalian et al. N Engl J Med 2012;2443-54. [4]Sznol et al. ASCO 2013, oral presentation, abs CRA9006.

Presented by: Jedd D. Wolchok, MD, PhD

Phase I Study: Schedule

Concurrent Cohorts



- First tumor assessment at 12 weeks

Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every 2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks

- **Tumor assessments by mWHO and immune-related response criteria**
- **Data as of Feb 2013 for 86 patients**

Presented by: Jedd D. Wolchok, MD, PhD

Treatment-Related Adverse Events (≥10% of all patients)

Treatment-Related Adverse Event Number of Patients (%)	Concurrent All Cohorts (n=53)		Sequenced All Cohorts (n=33)	
	All Gr	Gr 3-4	Al Gr	Gr 3-4
Any adverse event	**49 (93)**	**28 (53)**	**24 (73)**	**6 (18)**
Rash	**29 (55)**	**2 (4)**	**3 (9)**	**0**
Pruritus	**25 (47)**	**0**	**6 (18)**	**0**
Fatigue	**20 (38)**	**0**	**3 (9)**	**0**
Diarrhea	**18 (34)**	**3 (6)**	**3 (9)**	**0**
Nausea	**11 (21)**	**0**	**1 (3)**	**0**
Pyrexia	**11 (21)**	**0**	**1 (3)**	**0**
↑ AST	**11 (21)**	**7 (13)**	**0**	**0**
↑ ALT	**11 (21)**	**6 (11)**	**1 (3)**	**0**
↑ Lipase	**10 (19)**	**7 (13)**	**4 (12)**	**2 (6)**
↑ Amylase	**8 (15)**	**3 (6)**	**1 (3)**	**1 (3)**
Cough	**7 (13)**	**0**	**2 (6)**	**0**
Vomiting	**6 (11)**	**1 (2)**	**0**	**0**
Vitiligo	**6 (11)**	**0**	**0**	**0**
Headache	**6 (11)**	**0**	**0**	**0**

Presented by: Jedd D. Wolchok, MD, PhD

Treatment-Related Select Adverse Events Occurring in ≥1 Patient

Select Adverse Event Number of Patients (%)	Concurrent Regimen All Cohorts (n=53)		Sequenced Regimen All Cohorts (n=33)	
	All Gr	Gr 3-4	All Gr	Gr 3-4
Pulmonary	3 (6)	1 (2)	1 (3)	0
Renal	3 (6)	3 (6)	0	0
Endocrinopathies	7 (13)	1 (2)	3 (9)	2 (6)
Uveitis	3 (6)	2 (4)	0	0
Skin	37 (70)	2 (4)	8 (24)	0
Gastrointestinal	20 (38)	5 (9)	3 (9)	0
Hepatic	12 (23)	8 (15)	1 (3)	0
Infusion reaction	1 (2)	0	0	0
↑ Lipase	10 (19)	7 (13)	4 (12)	2 (6)
↑ Amylase	8 (15)	3 (6)	1 (3)	1 (3)

Presented by: Jedd D. Wolchok, MD, PhD

Safety Summary

Concurrent Treatment

- Grade 3-4 related adverse events occurred in 28 of 53 patients (53%), representing mostly tissue-specific inflammation
  - The most common were asymptomatic lab abnormalities: elevations of lipase (13% of patients), AST (13%), and ALT (11%)
- The 3 mg/kg nivolumab + 3 mg/kg ipilimumab cohort exceeded the MTD
  - 3 of 6 patients had DLTs of asymptomatic grade 3-4 elevated lipase that persisted ≥3 weeks
- Therefore, 1 mg/kg nivolumab + 3 mg/kg ipilimumab was chosen to move forward
- Eleven patients (21%) discontinued treatment due to related adverse events

Sequenced Treatment

- Grade 3-4 related adverse events occurred in 6 of 33 patients (18%)
  - The most common was asymptomatic elevation of lipase (2 patients, 6%)
- Three patients (9%) discontinued treatment due to related adverse events

- **Related adverse events were managed using standard protocol algorithms**
- **No treatment-related deaths were reported**

Presented by: Jedd D. Wolchok, MD, PhD

Clinical Activity: Concurrent Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	16 (31)

- With concurrent treatment of nivolumab + ipilimumab, 40% (range 21-53%) of patients had confirmed objective responses
- About one third of patients (31%) had rapid and deep tumor regressions

Presented by: Jedd D. Wolchok, MD, PhD

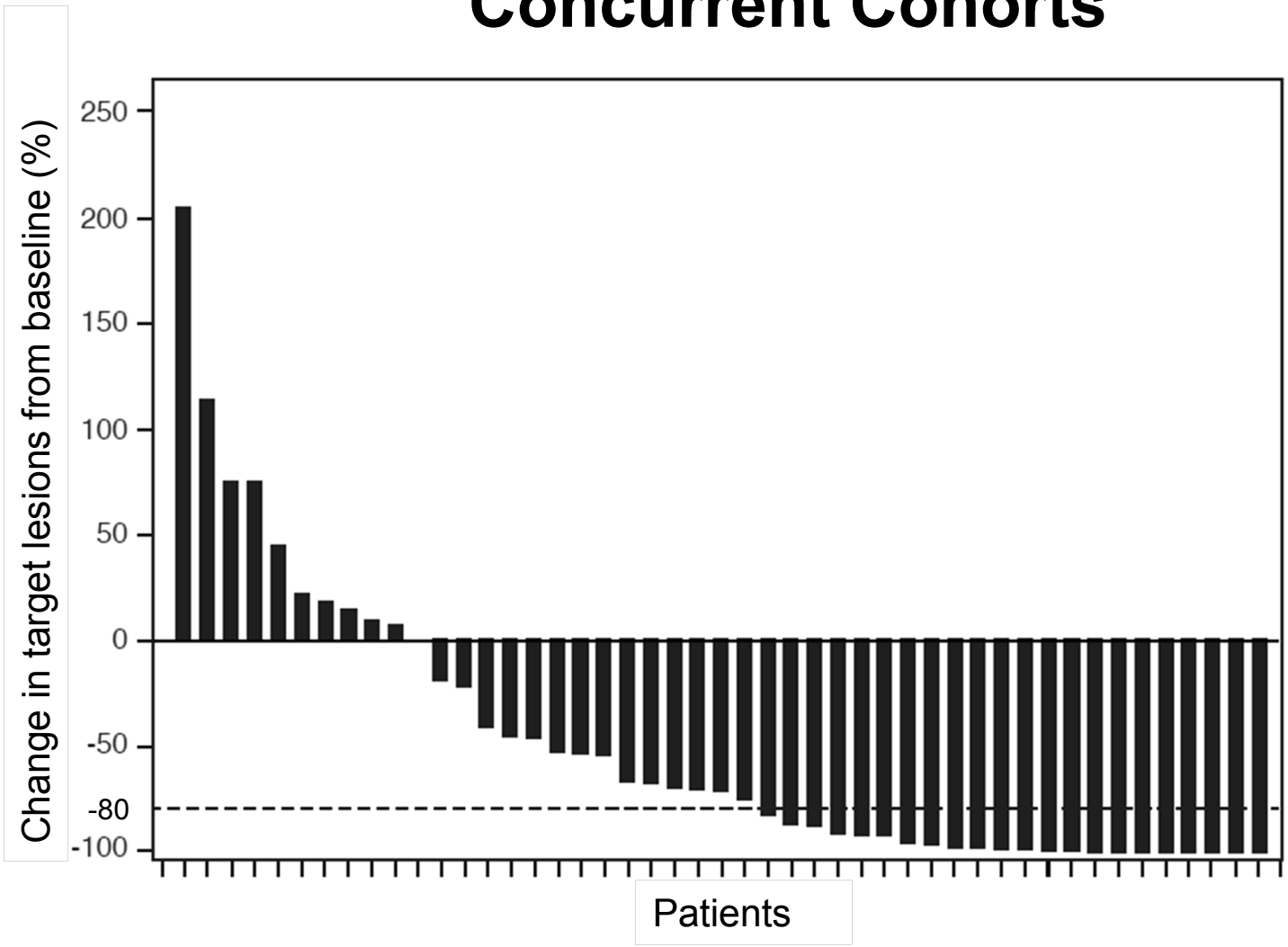
Clinical Activity: Concurrent Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	16 (31)

- With 1 mg/kg nivolumab + 3 mg/kb ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences

Presented by: Jedd D. Wolchok, MD, PhD

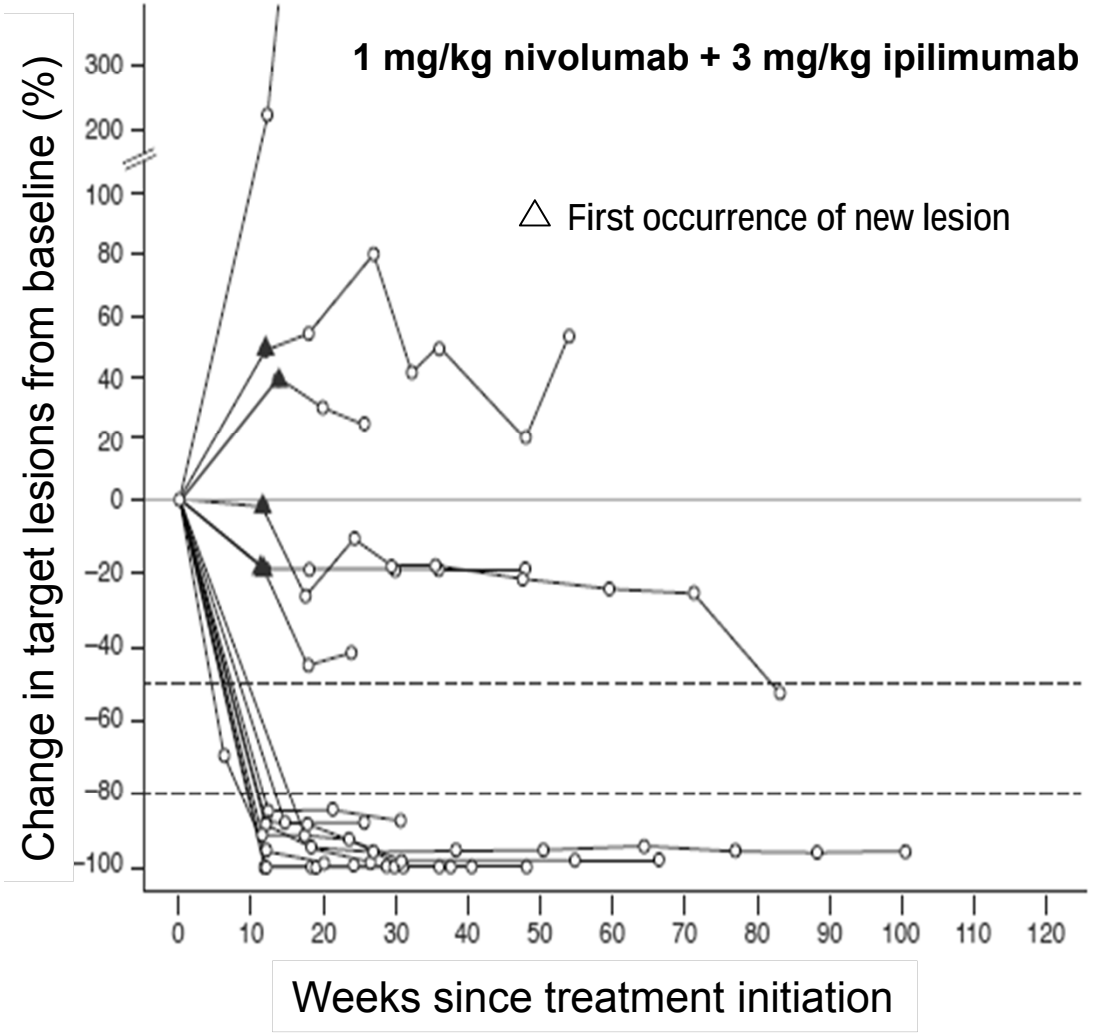
Best Responses in All Evaluable Patients in Concurrent Cohorts

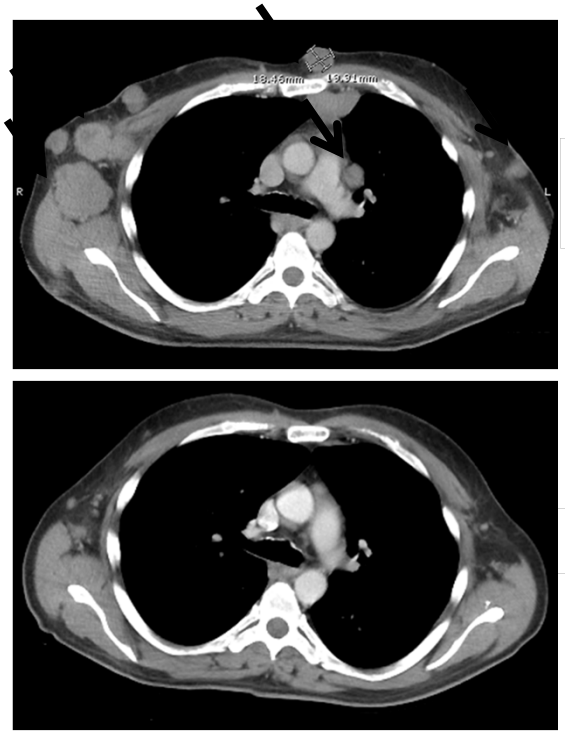


After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients continue to respond as of Feb 2013.

Presented by: Jedd D. Wolchok, MD, PhD

Rapid and Durable Changes in Target Lesions





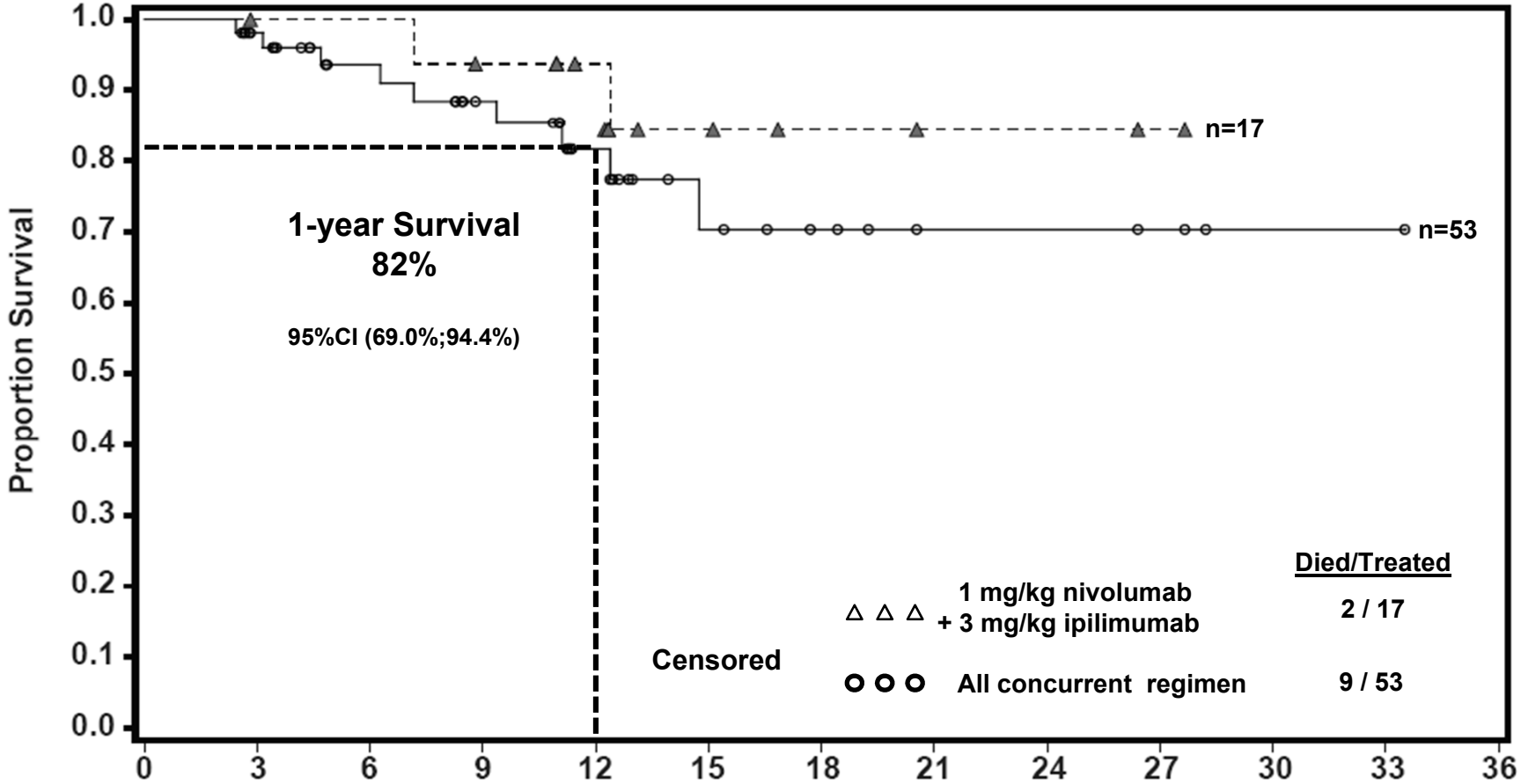
Pre-treatment

12 weeks

- **A 52-year-old patient presented with extensive nodal and visceral disease**
- **Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting**
- **Within 4 wk, LDH normalized and symptoms resolved**
- **At 12 wk, there was marked reduction in all areas of disease as shown**

Presented by: Jedd D. Wolchok, MD, PhD

Preliminary Survival of Patients Treated with the Concurrent Regimen



Patients at Risk

1 mg + 3 mg	17	16	16	14	10	5	3	2	2	1	0	0	0
All concurrent	53	47	36	29	19	10	7	4	4	3	1	1	0

Presented by: Jedd D. Wolchok, MD, PhD

Conclusions

- The concurrent combination of nivolumab and ipilimumab induced objective response rates appearing higher than published monotherapy values
- The nature of the responses appeared to be distinctly different from those of the nivolumab and ipilimumab monotherapies
  - Responses were rapid and deep
  - At the combined doses chosen for phase 3 study, all responding patients achieved deep or complete responses
- Treatment-related adverse events managed using standard protocols
  - No treatment-related deaths
- Clinical activity in patients who previously progressed on ipilimumab and then received nivolumab
- Based on these results, a phase 3 trial is open to investigate the efficacy of the concurrent nivolumab/ipilimumab combination vs. nivolumab vs. ipilimumab in patients with advanced melanoma (NCT01844505)
  - This combination is also being investigated in non-small-cell lung cancer and renal cell carcinoma

Presented by: Jedd D. Wolchok, MD, PhD

Abstract: 9011

Title: Phase I/II trial of PD-1 antibody nivolumab with peptide vaccine in patients naive to or that failed ipilimumab.

Track: Clinical Science Symposium, PD1/PDL1: An Effective Target in Melanoma

Authors: Jeffrey S. Weber, Ragini Reiney Kudchadkar, Geoffrey Thomas Gibney, Ronald C. De Conti, Bin Yu, Wenshi Wang, Amod Sarnaik, Alberto J Martinez, Jodi Kroeger, Cabell Eysmans, Donna Gallenstein, Xiuhua Zhao, Ann Chen; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Moffitt Cancer Center, Tampa, FL; Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Nivolumab, an IgG4 fully human monoclonal antibody against checkpoint protein PD-1, is active in metastatic melanoma, renal cell and non-small cell lung cancer. It was administered with a multi-peptide vaccine to patients (pts) with unresectable melanoma who failed at least one regimen for metastatic disease and were ipilimumab naïve, or failed ipilimumab, to assess the toxicity and tolerability of the combination and perform correlative immune assays. **Methods:** Three cohorts of 10 HLA A0201 positive ipilimumab-naïve pts received nivolumab at 1, 3 or 10 mg/kg, then three additional cohorts of pts who had failed prior ipilimumab received nivolumab at 3 mg/kg: two cohorts of 10 pts each who were A0201 positive and had either grade 2 or less ipilimumab toxicity, or grade 3 dose limiting ipilimumab toxicity; finally 40 pts were treated with antibody who had grade 2 or less ipilimumab toxicity and were not HLA restricted. Pre-treatment archived tumor tissue as well as pre- and post-treatment peripheral blood cells were collected. **Results:** Median age for all pts was 59;76% were M1c. Response rates by RECIST were 28% in 34 pts naïve to, and 32% for 46 pts who failed prior ipilimumab. Nivolumab did not induce the same irAEs in pts with prior ipilimumab induced toxicity. No cohort had more than one dose limiting toxicity. 2 pts had grade 3 pneumonitis. Three of ten pts who failed nivolumb had stable disease or a partial response to subsequent ipilimumab. Biomarker studies showed that elevated NY-ESO 1 and MART-1 specific CD8 T cells pre-treatment were associated with non-response ($p<0.005$ and <0.001), and that CTLA-4 positive CD4 T cells and T regulatory cells were elevated after treatment in non-responders ($p<0.01$). Immunohistochemical analysis of pre-treatment tumors indicated that PD-L1 staining was associated with response, but responses were also observed in pts whose tumors did not stain. **Conclusions:** Objective responses to nivolumab were observed after failing ipilimumab, and to ipilimumab after failing nivolumab. Elevation of CTLA-4 after nivolumab in non-responders suggest that sequential therapy with the combination should be tested. Tumor PD-L1 was associated with but not predictive of response. Clinical trial information: NCT01176461.

Phase I/II trial of PD-1 antibody nivolumab with peptide vaccine in patients naive to or that failed ipilimumab (#9011)

Weber, J.S., Kudchadkar, R., Yu, B., Gallenstein, D., *Horak, C., *Inzunza, H.D., Zhao, X., Martinez, A.J., Wang, W., Gibney, G., Kroeger, J., Eysmans, C., Sarnaik, A.A. and Chen, Y.A.

From Moffitt Cancer Center, Tampa, FL and *Bristol Myers Squibb, Princeton, NJ

Introduction

- Nivolumab: a fully human IgG_4 blocking antibody against programmed death-1 (PD-1)
- Clinical activity against melanoma, renal cell and non-small cell lung cancer*
- The current phase I trial tested nivolumab with a multi-peptide vaccine in patients with previously treated metastatic melanoma
- 90 patients in six cohorts received nivolumab with/without vaccine; cohorts 1-2-3 were ipilimumab naïve, and 4-5-6 were -refractory

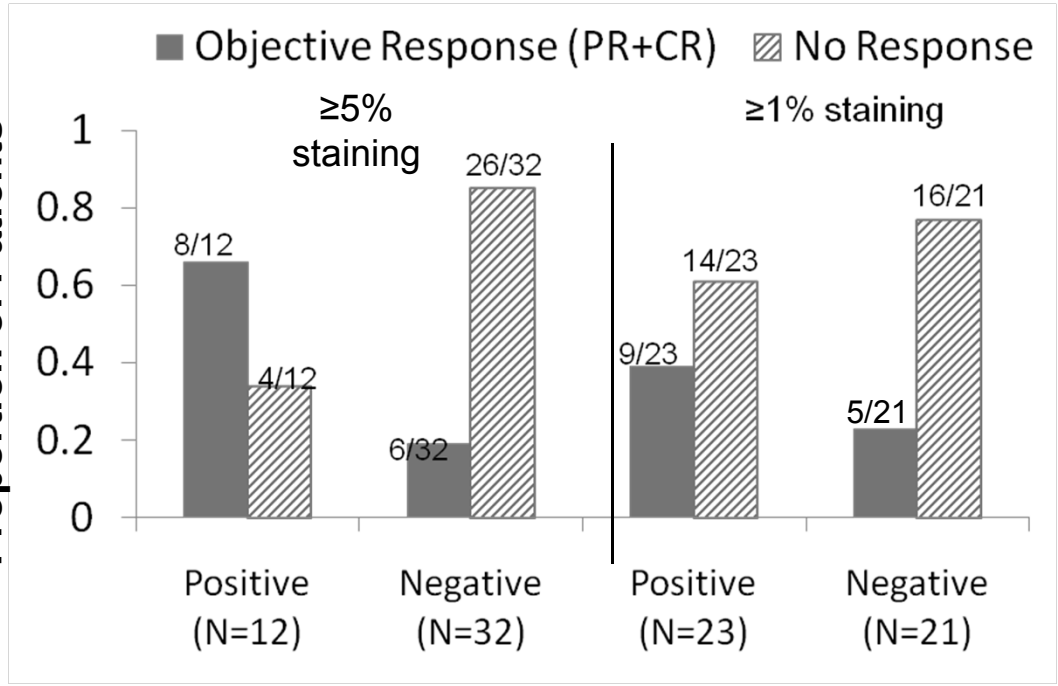
*Topalian , S et al, NEJM 2012

Peptide vaccine

- Included as an immune monitoring tool
- Peptides are all heteroclitic 9-10 aa epitopes:
  - NY-ESO-1 157-165 (165V)
  - MART-1 26-35 (27L)
  - gp100 209-217 (210M)
  - gp100 280-288 (288V)
  - All emulsified with Montanide ISA 51 VG
  - Dosed at 0.5 – 1 mg each subcutaneously

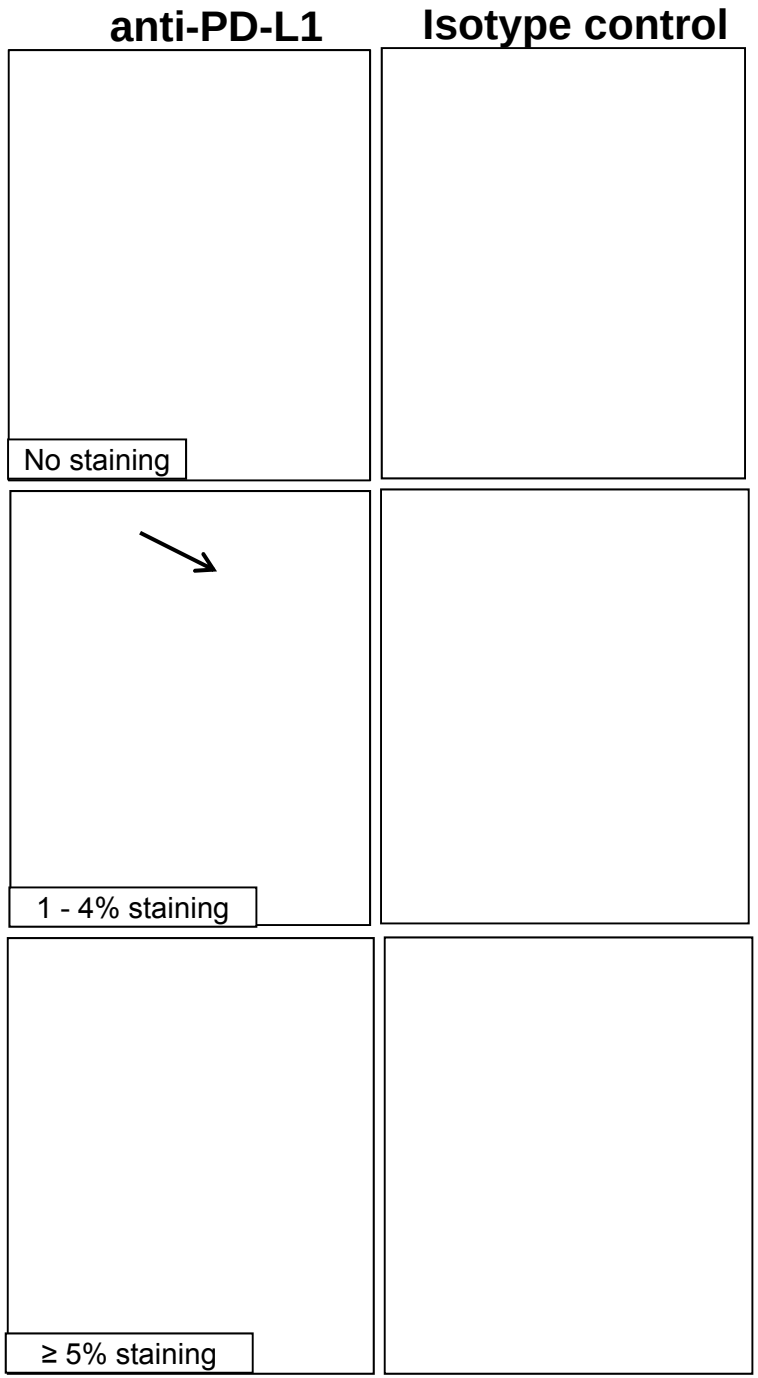
Clinical Efficacy

Dose of Nivolumab	Objective Response	Objective Response Rate, % (95% CI)	Response Duration, weeks	Stable Disease ≥ 24 weeks	Progression-Free Survival Rate at 24 weeks
Ipilimumab naïve patients					
1 mg/kg HLA A2+	3/10	30% (6.7 - 65.3%)	140+, 128+, 76+	2/10	50%
3 mg/kg HLA A2+	4/13	31% (9.1 - 61.4%)	84+, 36, 24, 24	1/13	39%
10 mg/kg HLA A2+	1/11	9% (0.2 - 41.3%)	84+	4/11	45%
Ipilimumab refractory patients					
3 mg/kg HLA A2+	3/10	30% (6.7 - 65.3%)	60+, 60+, 60+,	2/10	50%
3 mg/kg HLA A2+ with grade 3 irAE	1/5	20% (0.5 -71.6%)	36+	2/5	60%
3 mg/kg HLA unrestricted	10/38	26% (13.4 - 43.1%)	48+, 36+, 36+, 36+, 36+, 24+, 24+,24+, 24+, 12+	7/38	44%
All Cohorts	22/87	25% (16.6 - 35.8%)		18/87	46%



PD-L1 Status for 44 pts

Association between PD-L1 staining data & clinical response		
	PR+CR	**No Response**
PD-L1 positive		
≥ 5% staining (N=12)	67%	34%
≥ 1% staining (N=23)	39%	61%
PD-L1 negative		
< 5% staining (N=32)	19%	81%
< 1% staining (N=21)	23%	77%



Biomarkers

- Tumor membrane PD-L1 staining at 5% with an automated system is associated with response with p=0.004, but patients with PD-L1 negative tumors can respond
- Pre-treatment levels of antigen specific CD8 T cells and CTLA-4 on CD8 T cells are inversely associated with response
- PD-1 expression on CD4/CD8 T cells decreases with treatment

Conclusions

- The response rate to nivolumab in ipilimumab-refractory patients is 25%; CR+PR+SD is 46%
- Responses in ipilimumab naïve and –refractory patients can be long lasting – up to 33 months
- Nivolumab failures that are ipilimumab-naive can respond to subsequent ipilimumab
- The irAEs observed with prior ipilimumab are not recapitulated with nivolumab, even if grade 3
- PD-L1 tumor staining is not a reliable predictive marker for response to nivolumab using a 1% or 5% membrane cut-off with an automated system

Abstract: CRA9007

Title: Multicenter, randomized phase II trial of GM-CSF (GM) plus ipilimumab (Ipi) versus Ipi alone in metastatic melanoma: E1608.

Track: Oral Abstract Session, Melanoma/Skin Cancers

Authors: F. Stephen Hodi, Sandra J. Lee, David F. McDermott, Uma N. M. Rao, Lisa H. Butterfield, Ahmad A. Tarhini, Philip D. Leming, Igor Puzanov, John M. Kirkwood, Eastern Cooperative Oncology Group; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; University of Pittsburgh Physicians, Pittsburgh, PA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; University of Pittsburgh Medical Center, Pittsburgh, PA; Cincinnati Hematology Oncology, Inc., Cincinnati, OH; Vanderbilt University Medical Center, Nashville, TN

Background: CTLA-4 blockade and GM secreting tumor vaccine combinations demonstrate therapeutic synergy in multiple preclinical models. GM has activity in prostate and ovarian carcinoma and is being evaluated in phase III adjuvant trials for melanoma and lymphoma. GM enhances dendritic cell activation and potentiates antitumor T and B cell responses. GM may induce regulatory immune responses. A key issue is whether systemic GM might synergize with CTLA-4 blockade. **Methods:** Eligibility: measureable disease, ≤1 prior therapy, no CNS mets, ECOG PS 0-1, > 4 wks prior therapy, adequate end organ function, no autoimmune disease, no prior CTLA-4 blockade/CD137 agonist. OS was primary endpoint. Pts randomized to Arm A Ipi 10 mg/kg q3 wks IV x 4 then q12 wks plus GM 250 µg SC days 1-14 of 21 day cycles vs. Arm B Ipi 10 mg/kg as in Arm A alone. Due to known inflammatory effects of treatments, pts were permitted to continue up to 100% increase in SPD and four new lesions in absence of declining performance status and discretion of treating physician. Drug supply, funding from Sanofi/Bristol-Myers Squibb. **Results:** 245 pts were enrolled. Arms were balanced for demographics. Median follow up 13.3 mos. RR Arm A 11.3 % (6.1, 18.6), Arm B 14.7% (8.6,22.8) (not significant;NS). PFS Arm A 3 mos (2.9,4.3), Arm B 3.2 mos (3,4) (NS). Median OS Arm A not reached, Arm B 12.6 mos (9.2,-). One year OS for Arm A was 67.9% (59%,76%), Arm B 51.2% (42.6%, 61.3%) (stratified log rank p_1=0.016, p_2=0.033). HR for mortality on Ipi + GM/Ipi=0.65. Per study design (overall one-sided type I error 0.10), OS interim analysis was conducted at 69% info time. O'Brien-Fleming boundary was crossed for OS. Toxicity assessed for all cases regardless of eligibility. Gr 3-5 AEs 45% Arm A, 57% Arm B (p_2=0.078). Gr 5 AEs: Arm A colonic perforation (1), cardiac arrest (1); Arm B multiorgan failure (2), colonic perforation (2), hepatic failure (1), respiratory failure (2). **Conclusions:** Ipi plus GM significantly improves OS over Ipi alone. No significant differences in toxicity were observed. A trend toward improved tolerability is noted in the GM arm. Clinical trial information: NCT01134614.

Multicenter, Randomized Phase II Trial of GM-CSF (GM) plus Ipilimumab (Ipi) vs. Ipi Alone in Metastatic Melanoma: E1608

FS Hodi, S Lee, DF McDermott, UN Rao, LH Butterfield, AA Tarhini, P Leming, I Puzanov, JM Kirkwood

Dana-Farber Cancer Institute, Boston, MA; Beth Israel-Deaconess Medical Center, Boston ,MA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; The Christ Hospital, Cincinnati, OH, Vanderbilt University, Nashville, TN

Rationale for Combinatorial Approaches

- Combination of CTLA-4 blockade and GM-CSF secreting tumor cell vaccines has demonstrated therapeutic synergies in preclinical animal models

- Initial clinical experience of GVAX or GM-CSF + ipilimumab suggested synergistic biologic effects in melanoma, ovarian, and prostate cancer

- Concern GM-CSF may induce negative regulatory immune responses

Van Elsas et al. JEM; Hodi et al. PNAS 2003, 2008; Fong et al. Cancer Res 2009; Slingluff et al. CCR 2009

Randomized Phase II Trial of Ipilimumab plus GM-CSF versus Ipilimumab Alone
E1608

Randomization

- AJCC stage (Unresectable stage III, M1a/M1b, M1c)
- Prior therapy (none, IFN/IL-2/GM-CSF, One investigational therapy)

Arm A

Induction - Ipilimumab 10 mg/kg IV, Day 1 x 4 cycles
Maintenance - Ipilimumab 10 mg/kg IV, Day 1 every 4th cycle

Sargramostim (GM-CSF) 250 mcg SQ Q Day, Days 1-14 of 21 day cycle

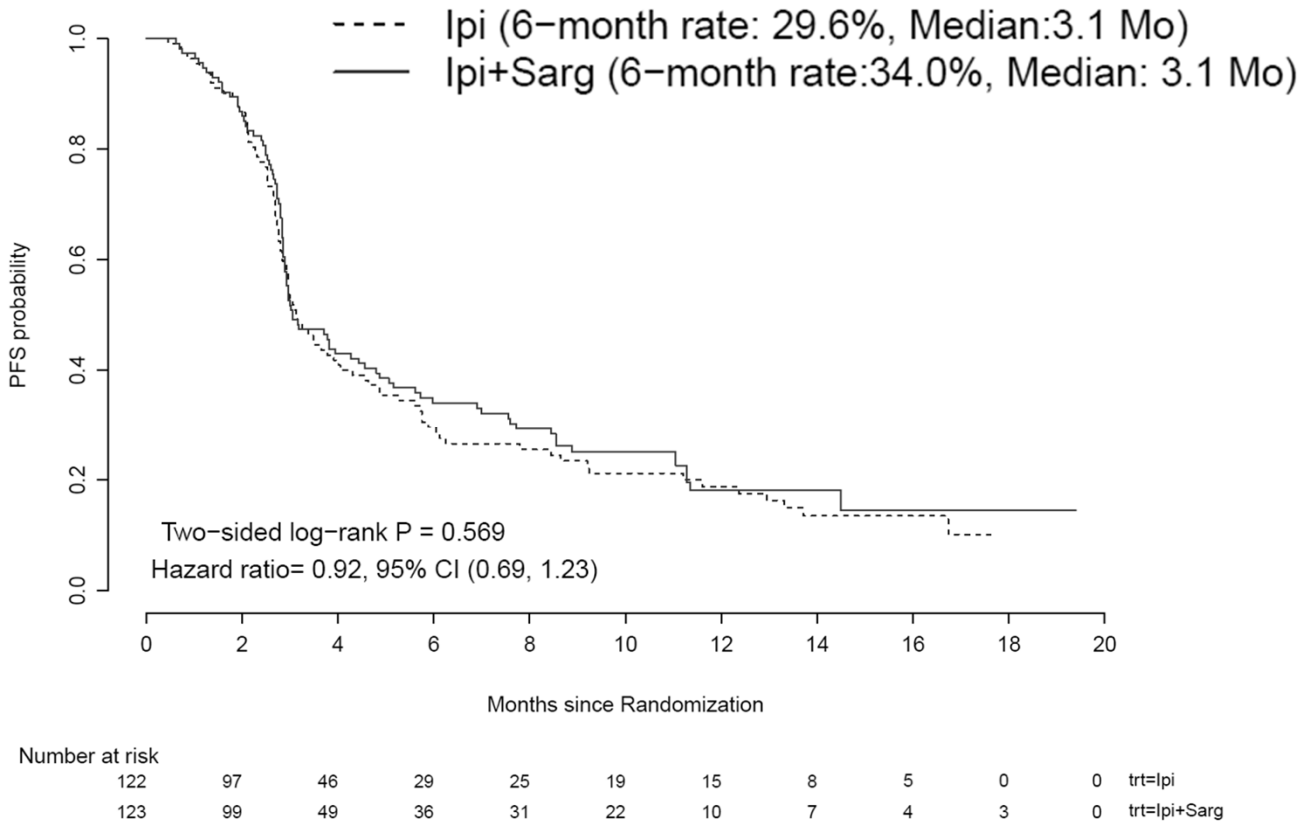
Arm B

Induction - Ipilimumab 10 mg/kg IV, Day 1 x 4 cycles
Maintenance - Ipilimumab 10 mg/kg IV, Day 1 every 4th cycle

Responses
RECIST

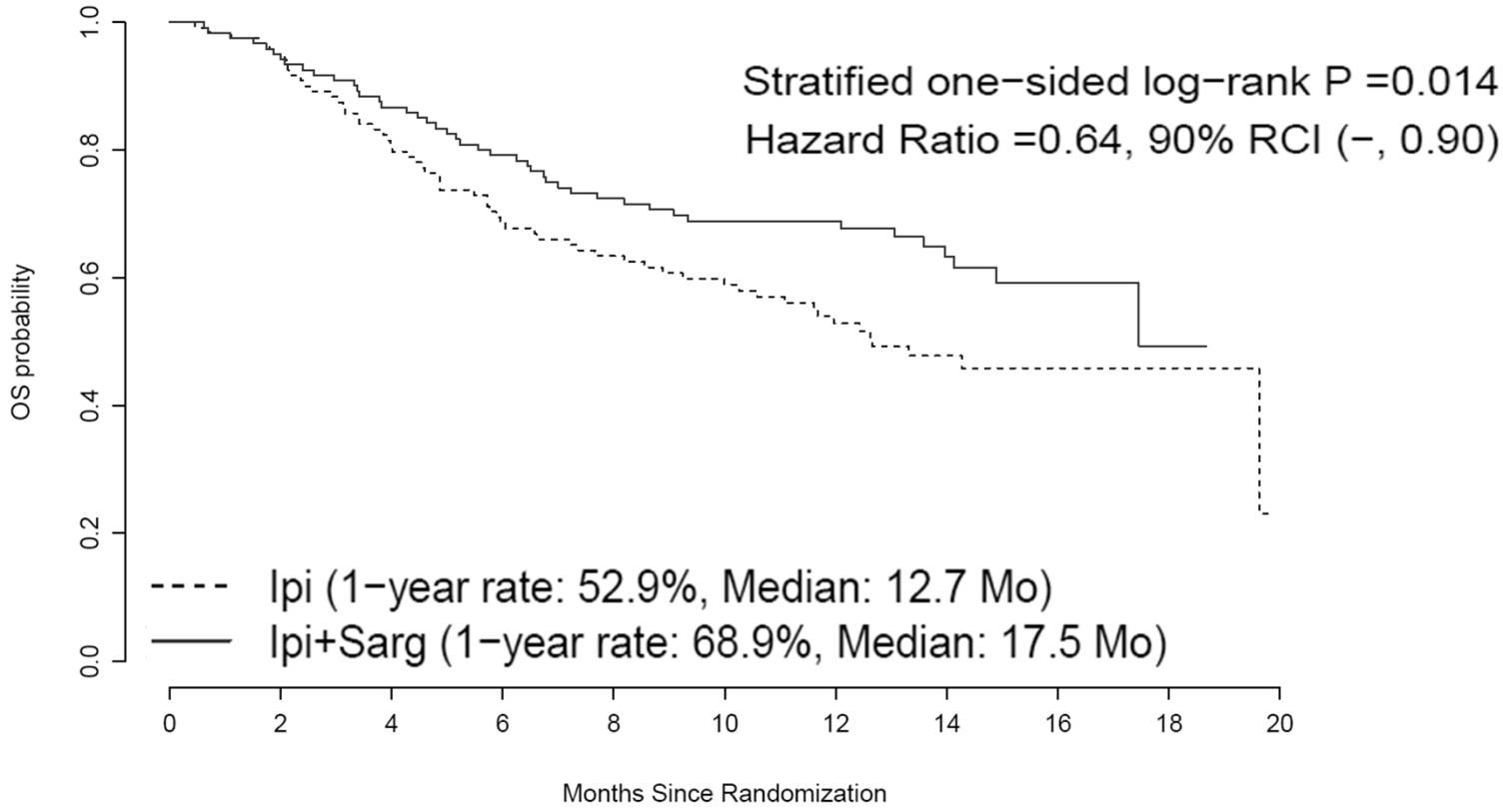
	Arm A: Ipi+Sarg (n=123)	Arm B: Ipi (n=122)	Comparisons
Clinical Response			
-CR	2 (1.6%)	0 (0%)	**P2=0.880 (Chi-square test)**
-PR	17 (13.8%)	18 (14.8%)	
-SD	26 (21.1%)	23 (18.9%)	
-PD	55 (44.7%)	52 (42.6%)	
-Uneval	20 (16.3%)	23 (18.9%)	
-Unknown	3 (2.4%)	6 (4.9%)	
Overall Response Rate (95% CI)	19/123 (15.5%) (9.6%, 23.1%)	18/122 (14.8%) (9.0%, 22.3%)	

Progression-Free Survival



	Arm A: Ipi+Sarg (n=123)	**Arm B: Ipi (n=122)**	**Comparisons**
Progression-Free Survival (PFS)			
-Median, (95%CI)	3.1 mo (2.9, 4.6)	3.1 mo (2.9, 4.0)	P_2=0.569 (Log rank test)
- 6-mo PFS rate (95% CI)	34.0% (25.3,42.8)	29.6% (21.1,38.1)	
-HR (95% CI)	0.92 (0.69,1.23)	Reference	P_2= 0.571 (Cox model)

Overall Survival



Number at risk

122	114	94	80	72	64	49	28	14	6	0	trt=Ipi
123	115	104	94	84	75	63	39	11	2	0	trt=Ipi+Sarg

	Arm A: Ipi+Sarg (n=123)	**Arm B: Ipi (n=122)**	**Comparisons**
Overall Survival (OS)			
- Median , (95% CI)	17.5 mo (14.9, NR)	12.7 mo (10.0, NR)	P1*=0.014 (Stratified Logrank test)
- 1-Year OS rate, (95% CI)	68.9% (60.6, 85.5)	52.9% (43.6, 62.2)	
- HR 90% RCI for HR	0.64 (-, 0.90)	Reference	P1* =0.014 (Stratified Cox model)

Tolerability and Safety

- The addition of sargramostim to ipilimumab decreased the incidence of high grade adverse events

- The addition of sargramostim to ipilimumab specifically improved pulmonary and gastrointestinal high grade events

Summary

- The addition of sargramostim to ipilimumab improves overall survival without impacting progression-free survival

- The addition of sargramostim decreases the incidence of high grade adverse events, particularly GI (perforation) and pulmonary with an overall favorable safety profile

Considerations

- Immediate clinical implications
- Ipilimumab 10 mg/kg (maintenance) versus 3 mg/kg
- Future development of cytokine and immune checkpoint blockade combinations

Intralesional Therapy/Oncolytic Virus

Abstract LBA 9008

Abstract: LBA9008

Title: OPTiM: A randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma.

Track: Oral Abstract Session, Melanoma/Skin Cancers

Authors: Robert Hans Ingemar Andtbacka, Frances A. Collichio, Thomas Amatruda, Neil N. Senzer, Jason Chesney, Keith A. Delman, Lynn E. Spitler, Igor Puzanov, Susan Doleman, Yining Ye, Ari M. Vanderwalde, Robert Coffin, Howard Kaufman; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; The University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC; Hubert H. Humphrey Cancer Center, Robbinsdale, MN; Mary Crowley Cancer Research Center, Dallas, TX; University of Louisville, Louisville, KY; Department of Surgery, Emory University, Atlanta, GA; Northern California Melanoma Center, San Francisco, CA; Vanderbilt University Medical Center, Nashville, TN; Amgen, Inc., Woburn, MA; Department of Biostatistics and Epidemiology, Amgen Inc., South San Francisco, CA; Amgen, Inc., Thousand Oaks, CA; Rush University Medical Center, Chicago, IL

Background: T-VEC is an oncolytic immunotherapy (OI) derived from herpes simplex virus type-1 designed to selectively replicate within tumors and to produce GM-CSF to enhance systemic antitumor immune responses. OPTiM is a randomized, phase III trial of T-VEC or GM-CSF in patients (pts) with unresected melanoma with regional or distant metastases. We report the primary results of the first phase III study of OI. **Methods:** Key criteria: age ≥18 yrs; ECOG ≤1; unresectable melanoma stage IIIB/C or IV; injectable cutaneous, SC, or nodal lesions; LDH ≤1.5X upper limit of normal; ≤3 visceral lesions (excluding lung), none >3 cm. Pts were randomized 2:1 to intralesional T-VEC (initially ≤ 4 mL x10^6 pfu/mL then after 3 wks, ≤ 4 mL x10^8 pfu/mL Q2W) or SC GM-CSF (125 µg/m^2qd x 14 days q28d). The primary endpoint was durable response rate (DRR): partial or complete response (CR) continuously for ≥6 mos starting within 12 mos. Responses were per modified WHO by blinded central review. A planned interim analysis of overall survival (OS; key secondary endpoint) was performed. **Results:** 436 pts are in the ITT set: 295 (68%) T-VEC, 141 (32%) GM-CSF. 57% were men; median age was 63 yrs. Stage distribution was: IIIB/C 30%, IVM1a 27%, IVM1b 21%, IVM1c 22%. Objective response rate with T-VEC was 26% (95% CI: 21%, 32%) with 11% CR, and with GM-CSF was 6% (95% CI: 2%, 10%) with 1% CR. DRR for T-VEC was 16% (95% CI: 12%, 21%) and 2% for GM-CSF (95% CI: 0%, 5%), p<0.0001. DRR by stage (T-VEC, GM-CSF) was IIIB/C (33%, 0%), M1a (16%, 2%), M1b (3%, 4%), and M1c (8%, 3%). Interim OS showed a trend in favor of T-VEC; HR 0.79 (95% CI: 0.61, 1.02). Most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia. Serious AEs occurred in 26% of T-VEC and 13% of GM-CSF pts. No ≥ grade 3 AE occurred in ≥ 3% of pts in either arm. **Conclusions:** T-VEC demonstrated both a statistically significant improvement in DRR over GM-CSF in pts with unresectable stage IIIB-IV melanoma and a tolerable safety profile; an interim analysis showed a trend toward improved OS. T-VEC represents a novel potential tx option for melanoma with regional or distant metastases. Clinical trial information: NCT00769704.

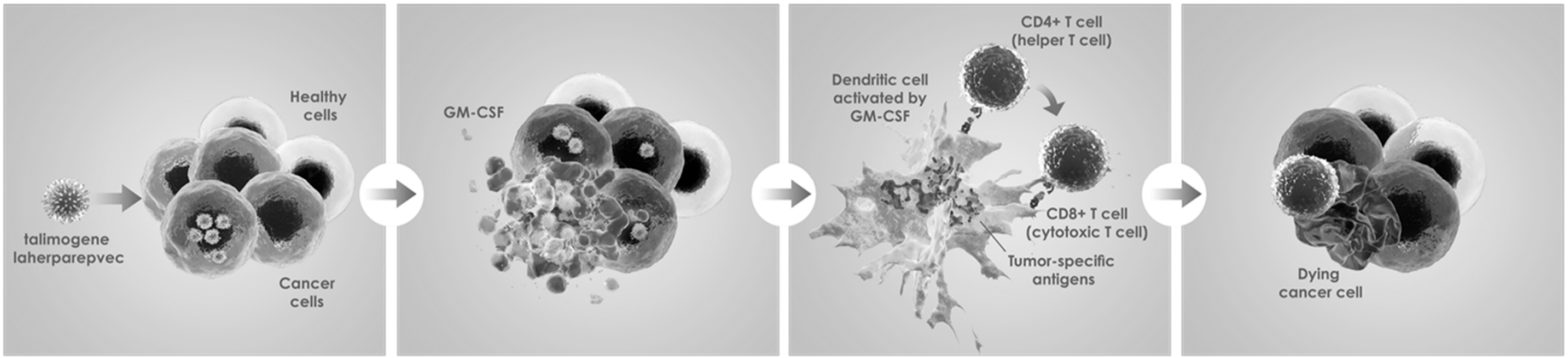
OPTiM: A Randomized Phase 3 Trial Of Talimogene Laherparepvec (T-VEC) Vs Subcutaneous Granulocyte-macrophage Colony-stimulating Factor (GM-CSF) For The Treatment Of Unresected Stage IIIB/C And IV Melanoma

Robert H.I. Andtbacka,[1] Frances Collichio,[2] Thomas Amatruda,[3] Neil Senzer,[4] Jason Chesney,[5] Keith A. Delman,[6] Lynn E. Spitler,[7] Igor Puzanov,[8] Susan Doleman,[9] Yining Ye,[10] Ari VanderWalde,[10] Robert Coffin,[9] Howard L. Kaufman[11]

[1]Huntsman Cancer Institute University of Utah, Salt Lake City, UT; [2]University of North Carolina Medical Center, Chapel Hill, NC; [3]Hubert Humphrey Cancer Center, Robbinsdale, MN; [4]Mary Crowley Cancer Research Center, Dallas, TX; [5]University of Louisville, Louisville KY; [6]Emory University, Atlanta, GA; [7]Northern California Melanoma Center, San Francisco, CA; [8]Vanderbilt University, Nashville, TN; [9]Amgen, Woburn, MA;[10]Amgen Inc., Thousand Oaks, CA; [11]Rush University Medical Center, Chicago, IL

T-VEC: An HSV-1 Derived Oncolytic Immunotherapy Designed to Produce Both Local and Systemic Effects

Local Effect: Tumor Cell Lysis → **Systemic Effect: Tumor-Specific Immune Response**



Selective viral replication in tumor tissue

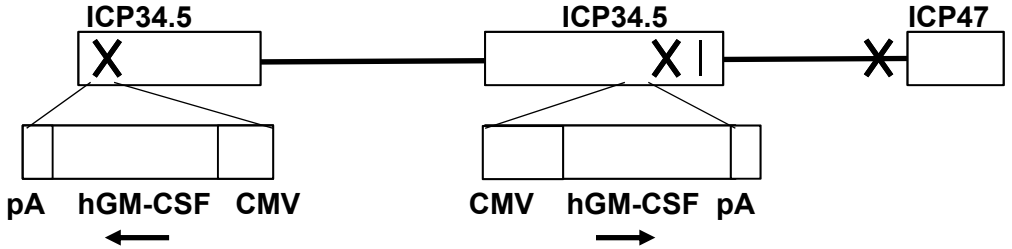
Tumor cells rupture for an oncolytic effect

Systemic tumor-specific immune response

Death of distant cancer cells

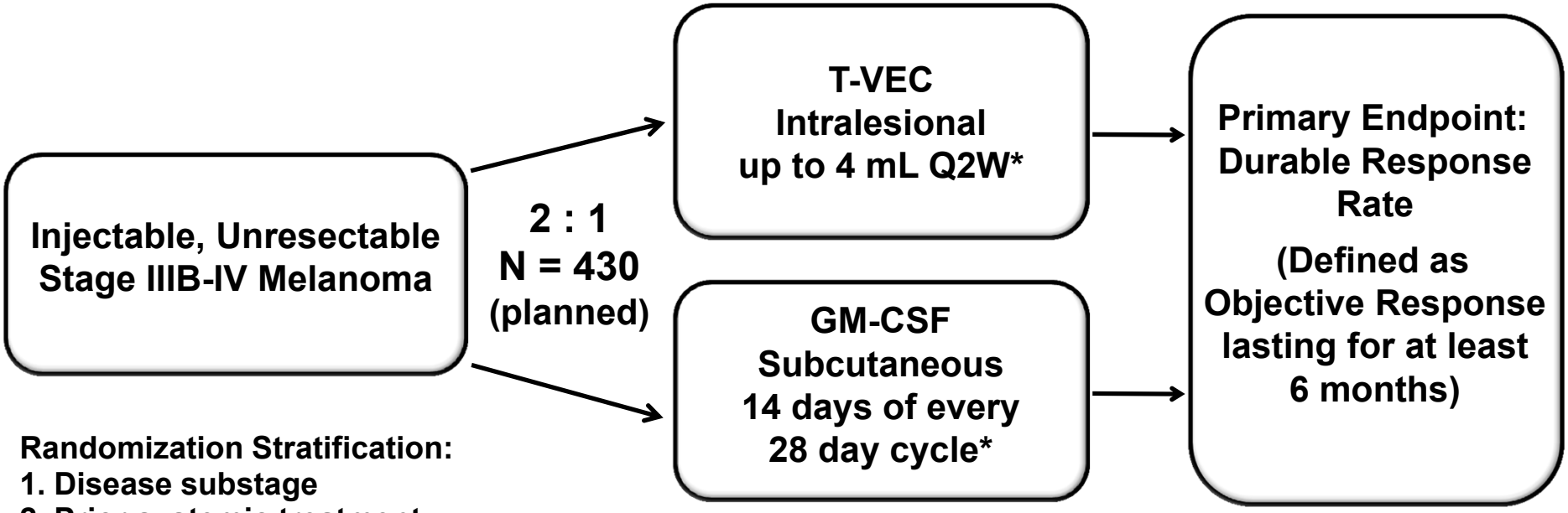
T-VEC key genetic modifications:

JS1/ICP34.5-/ICP47-/hGM-CSF



1. Varghese S, et al. *Cancer Gene Ther*. 2002;9:967-978. 2. Hawkins LK, et al. *Lancet Oncol*. 2002;3:17-26. 3. Fukuhara H, et al. *Curr Cancer Drug Targets*. 2007;7:149-155. 4. Sobol PT, et al. *Mol Ther*. 2011;19:335-344. 5. Liu BL, et al. *Gene Ther*. 2003;10:292-303. 6. Melcher A, et al. *Mol Ther*. 2011;19:1008-1016. 7. Fagoaga OR In: McPherson RA, Pincus MR, eds. Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd ed. Philadelphia, PA: Elsevier; 2011:933-953. 8. Dranoff G. *Oncogene*. 2003;22:3188-3192.

OPTiM Phase III Study Design



Randomization Stratification:
1. Disease substage
2. Prior systemic treatment
3. Site of disease at first recurrence
4. Presence of liver metastases

Patients were to remain on treatment beyond progression unless clinically significant (ie, associated with reduced performance status) after 24 weeks

* Dosing of intralesional T-VEC was ≤ 4 mL x10^6 pfu/mL once, then after 3 weeks, ≤ 4 mL x10^8 pfu/mL Q2W. Dosing of GM-CSF was 125 µg/m^2 subcutaneous daily x14 days of every 28 day cycle.

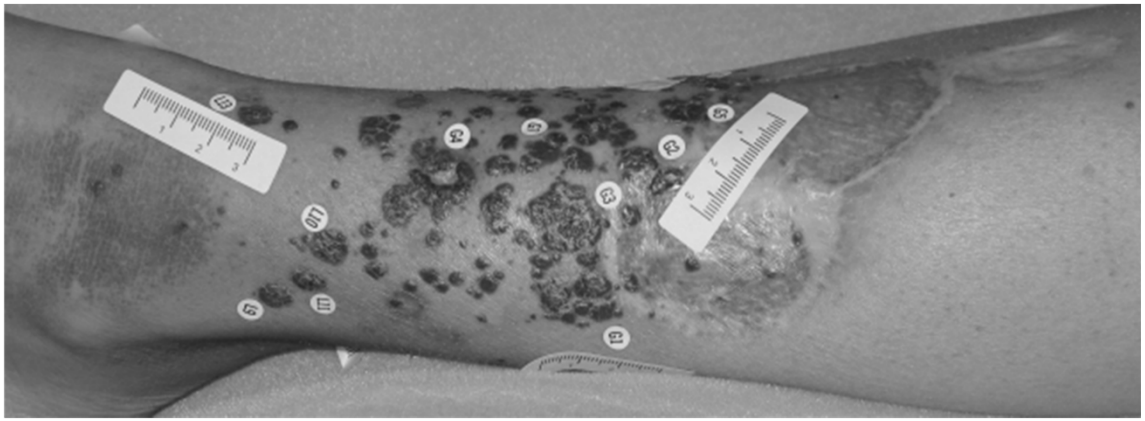
Primary Endpoint: Durable Response Rate per EAC
Secondary Endpoint: Objective Response per EAC

ITT Set	GM-CSF (N=141)	T-VEC (N= 295)	Unadjusted Odds Ratio
Durable Response Rate	2.1%	16.3%	8.9 95% CI: (2.7, 29.2) *P* < 0.0001

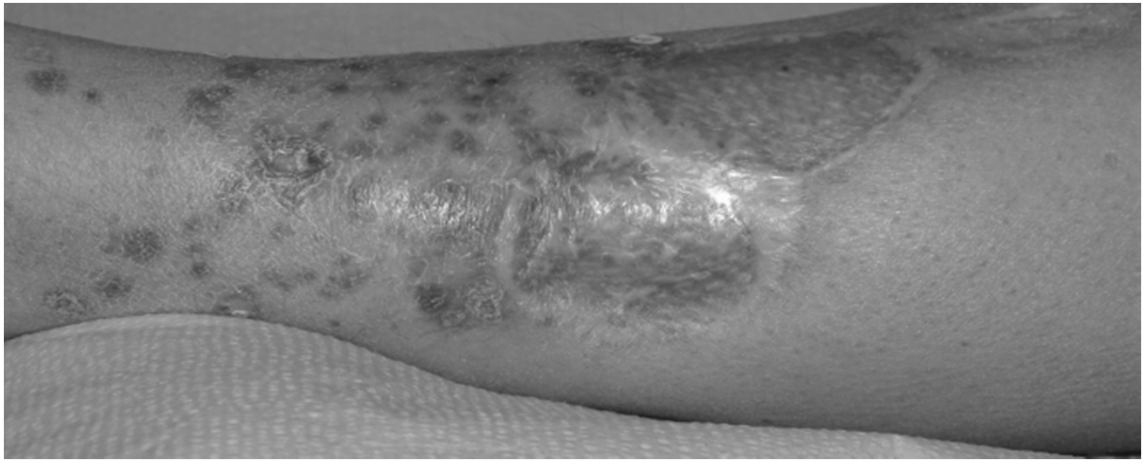
ITT Set	GM-CSF (N=141)	T-VEC (N= 295)
Objective Overall Response (95% CI)	5.7% (1.9, 9.5)	26.4% (21.4, 31.5)
CR	0.7%	10.8%
PR	5.0%	15.6%

T-VEC Responses in Injected And Uninjected Lesions

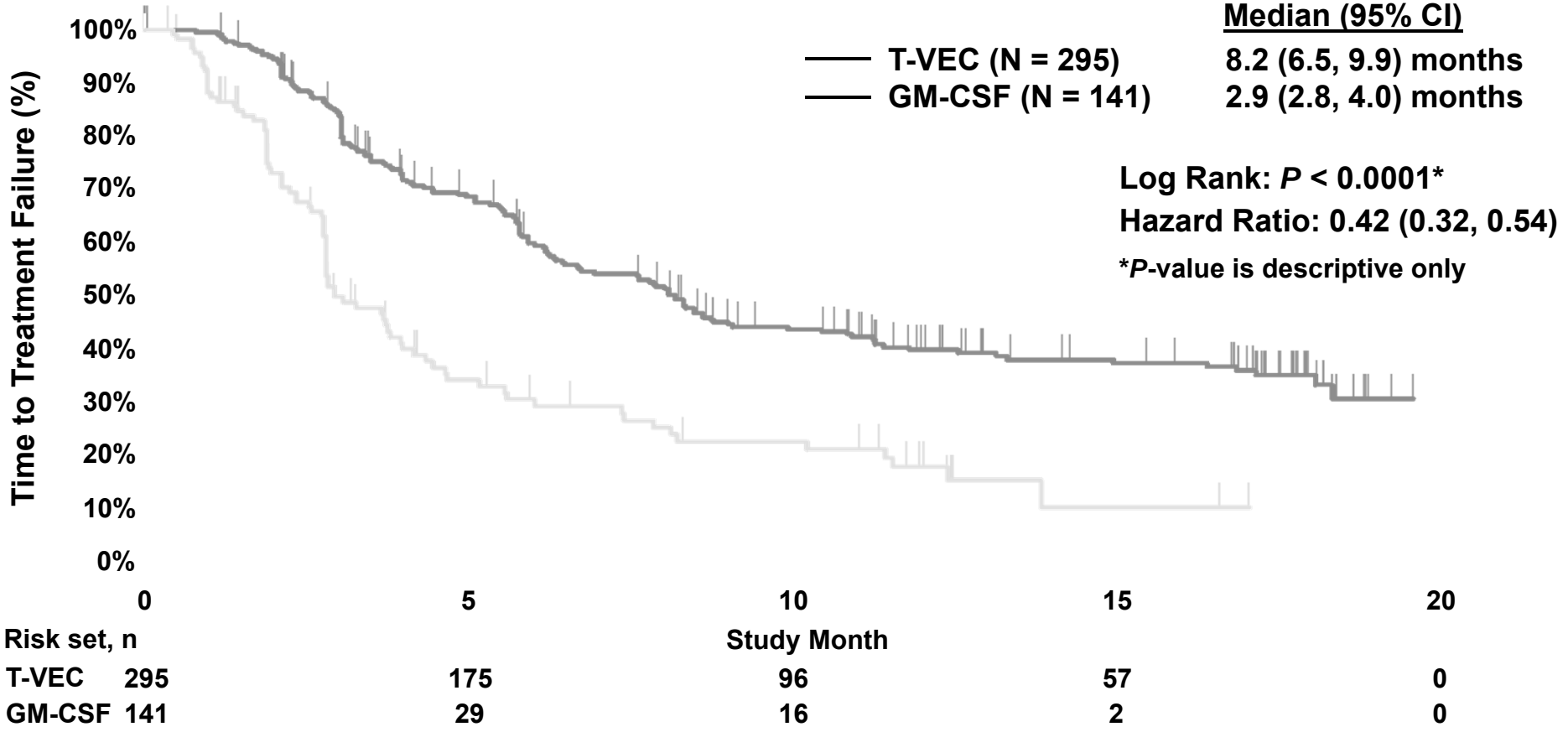
Cycle 1



Cycle 13

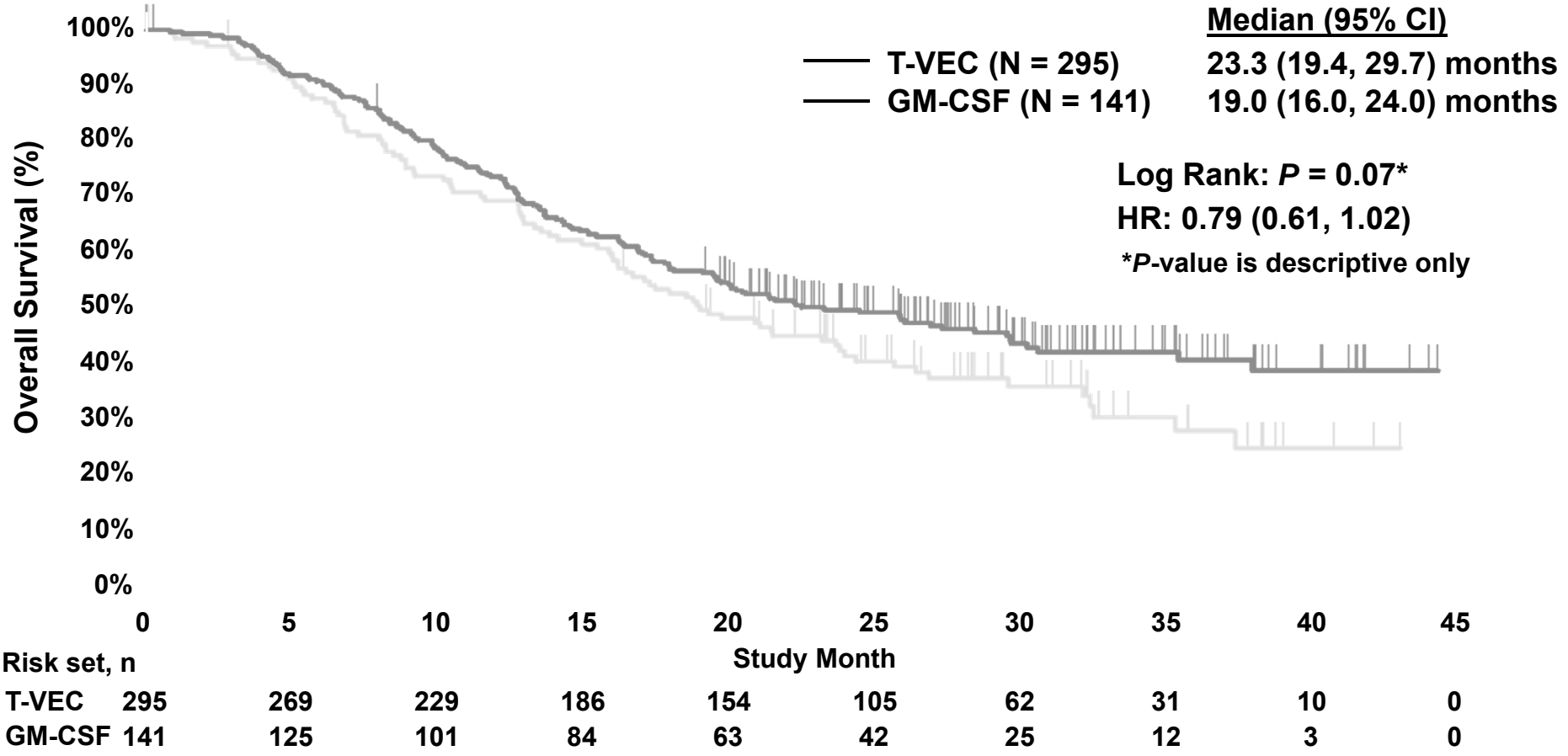


Secondary Endpoint: Time to Treatment Failure



- Time to treatment failure was defined as time from the first dose of study treatment until death or development of clinically significant progressive disease (PD) per investigator for which no objective response was subsequently achieved
- Patients who withdrew prior to development of clinically significant PD were censored at the time of the last assessment

Interim Overall Survival



Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-month	73.7%	69.4%	4.3 (-4.9, 13.5)
24-month	49.6%	41.3%	8.3 (-1.9, 18.5)
36-month	40.6%	27.8%	12.8 (1.0, 24.6)

- Interim OS data represent >85% (250 of 290) of the required events for the primary analysis of OS
- 290 events required to demonstrate a OS HR of 0.67 with 90% power

Safety: Adverse Events (AEs)

AEs of All Grades Occurring in ≥ 20% of T-VEC Treated Patients

Preferred Term- % All Grade AEs	GM-CSF (N=127)	T-VEC (N=292)
Fatigue	36.2%	50.3%
Chills	8.7%	48.6%
Pyrexia	8.7%	42.8%
Nausea	19.7%	35.6%
Influenza-like illness	15.0%	30.5%
Injection site pain	6.3%	27.7%
Vomiting	9.4%	21.2%

Grade 3/4 AEs Occurring in ≥ 5 Patients in Either Arm

Preferred Term- % All Grade AEs	GM-CSF (N=127)	T-VEC (N=292)
Cellulitis	<1%	2.1%
Fatigue	<1%	1.7%
Vomiting	0	1.7%
Dehydration	0	1.7%
Deep vein thrombosis	0	1.7%
Tumor pain	0	1.7%

Of 10 total fatal AEs on the T-VEC arm, 8 were due to PD. The only 2 fatal AEs on the T-VEC arm not associated with PD were sepsis (in the setting of cholangitis) and myocardial infarction.
No treatment-related fatal AEs were observed.

CONCLUSIONS

- **OPTiM met the study primary endpoint**
- **T-VEC significantly improved DRR vs GM-CSF in patients with unresected Stage IIIB-IV melanoma with limited visceral disease**
  - **(16% vs 2%, *P* < 0.0001)**
- **T-VEC is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a Phase III trial**
- **T-VEC has a tolerable safety profile. The only grade 3/4 AE that occurred in > 2% of patients was cellulitis (2.1%)**
- **Trend toward improved OS was seen with T-VEC at interim analysis**
  - **Primary OS analysis is pending**

Uveal Melanoma

CRA9003

Abstract: CRA9003

Title: Phase II study of selumetinib (sel) versus temozolomide (TMZ) in gnaq/Gna11 (Gq/11) mutant (mut) uveal melanoma (UM).

Track: Oral Abstract Session, Melanoma/Skin Cancers

Authors: Richard D. Carvajal, Jeffrey Alan Sosman, Fernando Quevedo, Mohammed M. Milhem, Anthony Michael Joshua, Ragini Reiney Kudchadkar, Gerald P. Linette, Thomas Gajewski, Jose Lutzky, David H. Lawson, Christopher D. Lao, Patrick J. Flynn, Mark R. Albertini, Takami Sato, Daniel Paucar, Katherine S. Panageas, Mark Andrew Dickson, Jedd D. Wolchok, Paul B. Chapman, Gary K. Schwartz; Memorial Sloan-Kettering Cancer Center, New York, NY; Vanderbilt University Medical Center, Nashville, TN; Mayo Clinic, Rochester, MN; University of Iowa Hospital and Clinics, Iowa City, IA; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Washington University in St. Louis, St. Louis, MO; The University of Chicago, Chicago, IL; Mount Sinai Comprehensive Cancer Center, Miami Beach, FL; Emory University School of Medicine, Atlanta, GA; University of Michigan, Ann Arbor, MI; Metro Minnesota Community Clinical Oncology Program, St. Louis Park, MN; University of Wisconsin, Madison, WI; Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Gq/11 mutations are early oncogenic events in UM resulting in MAPK pathway activation. We demonstrated decreased viability in UM cell lines harboring Gq/11 mut with sel, a small molecule inhibitor of MEK1/2 (Ambrosini, CCR 2012). **Methods:** We conducted a 16 center randomized phase II study of hyd-sulfate sel 75 mg BID vs TMZ 150 mg/m^2 daily for 5 days in 28-day cycles (or DTIC 1000 mg/m^2 q21 days) for patients (pts) with metastatic UM with a Q209 Gq/11 mut who have not received prior TMZ/DTIC. The primary endpoint was progression free survival (PFS). Secondary endpoints included overall survival (OS) and response rate (RR). Select pts underwent tumor biopsies at baseline and after 14 (+/- 3 days) of sel. Our statistical plan required ≥80 pts randomized and ≥68 events to detect a PFS hazard ratio of 0.6 (p=0.1). Randomization was stratified by mut (Gq vs G11), M stage and number of prior therapies (tx). Tumor assessment occurred every 4 weeks (wks) for 8 wks and then every 8 wks using RECIST 1.1. Pts receiving TMZ who progressed could receive sel (TMZ→sel). **Results:** 80 pts were randomized. Sel (n=39): median age 66 (range 32-86), 54% male, 54% G11 mut, median ECOG PS 0 (range 0-1), 97% M1c, median prior tx 0 (range 0-2). TMZ (n=41): median age 60 (range 34-81), 63% male, 58% G11 mut, median ECOG PS 0 (range 0-1), 93% M1c, median prior tx 0 (range 0-2). 11/39 (28%) pts on sel experienced grade (gr) 3 toxicity (tox) manageable with dose modification (5 CPK elevation, 3 LFT elevation, 1 rash, 1 lymphopenia, 1 edema). 1/41 (2%) pt on TMZ experienced gr 3 tox (neutropenia). No gr 4/5 tox occurred. 28 pts on sel underwent paired tumor biopsies with inhibition of pERK and cyclinD1 observed by Western blot at day 14. At interim analysis (9/25/12), 55 pts were evaluable with 45 progression events and 16 deaths. Sel (n=27): median PFS 16 wks (95% CI 8-30.9), RR 11%, median OS 11.8 months (95% CI 4.8-not reached). TMZ (n=28): median PFS 4 wks (95% CI 3.7-15), RR 0%, median OS 4.7 months (95% CI 4.3-14.3). TMZ→sel (n=25): median PFS 8.1 wks (95% CI 7-15), RR 0%. **Conclusions:** Sel is the first drug to ever show improved clinical activity in UM relative to TMZ. Sustained target inhibition is observed with sel. Final results will be presented. Clinical trial information: NCT01143402.

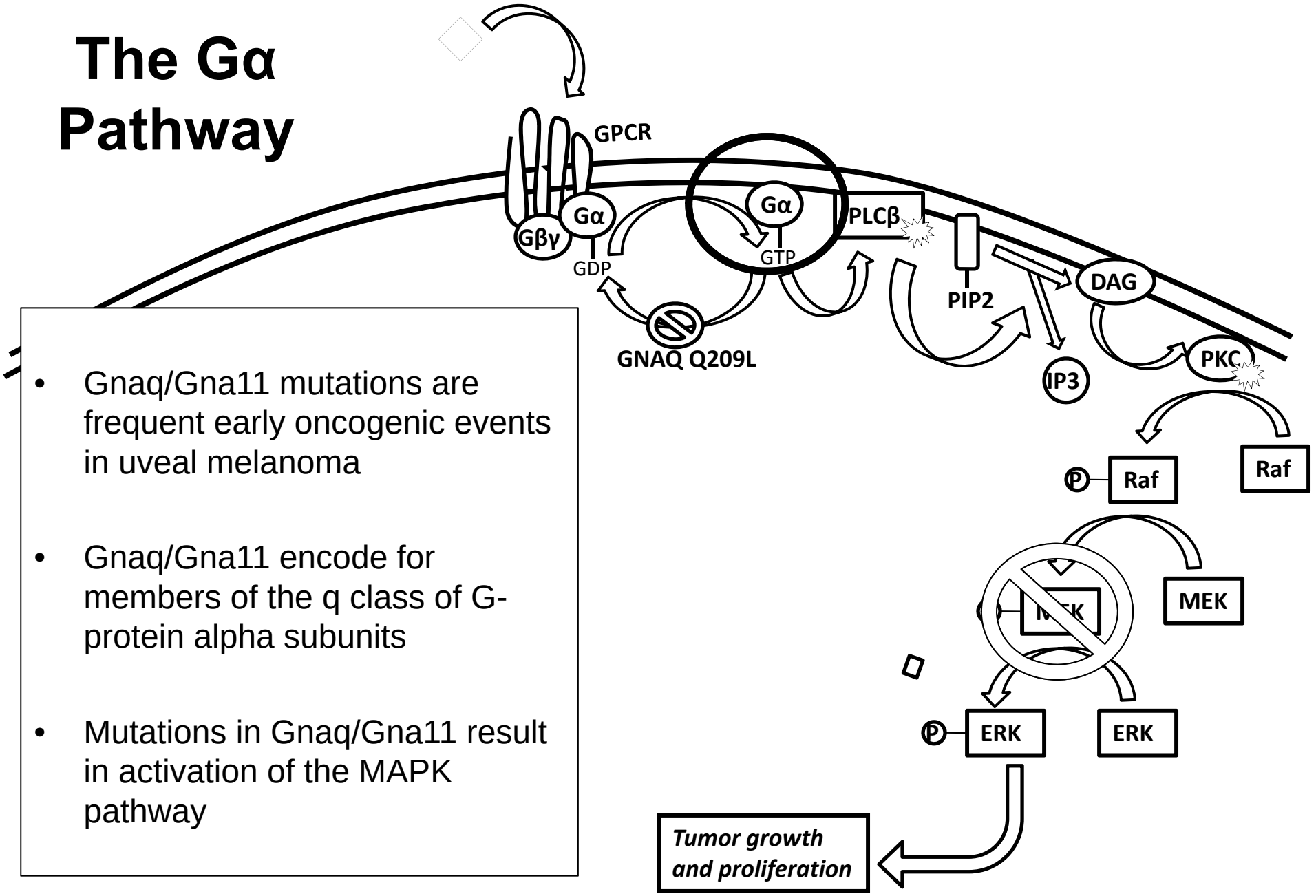
Phase II Study of Selumetinib vs Temozolomide in Patients with Advanced Uveal Melanoma (CTEP #8443)

Richard D. Carvajal
Memorial Sloan-Kettering Cancer Center

Jeffrey A. Sosman,[1] Fernando Quevedo,[2] Mohammed M. Milhelm,[3] Anthony M. Joshua,[4] Ragini R. Kudchadkar,[5] Gerald P. Linette,[6] Thomas Gajewski,[7] Jose Lutzky,[8] David Lawson,[9] Christopher D. Lao,[10] Patrick J. Flynn,[11] Mark R. Albertini,[12] Takami Sato,[13] Daniel Paucar,[14] Katherine S. Panageas,[14] Mark A. Dickson,[14] Jedd D. Wolchok,[14] Paul B. Chapman,[14] Gary K. Schwartz[14]

[1]Vanderbilt University, [2]Mayo Clinic, [3]University of Iowa, [4]Princess Margaret Cancer Center, [5]H Lee Moffitt Cancer Center, [6]Washington University, [7]University of Chicago, [8]Mt. Sinai Comprehensive Cancer Center, [9]Emory University, [10]University of Michigan, [11]Metro Minnesota CCOP, [12]University of Wisconsin, [13]Thomas Jefferson University, [14]Memorial Sloan-Kettering Cancer Center

The Gα Pathway



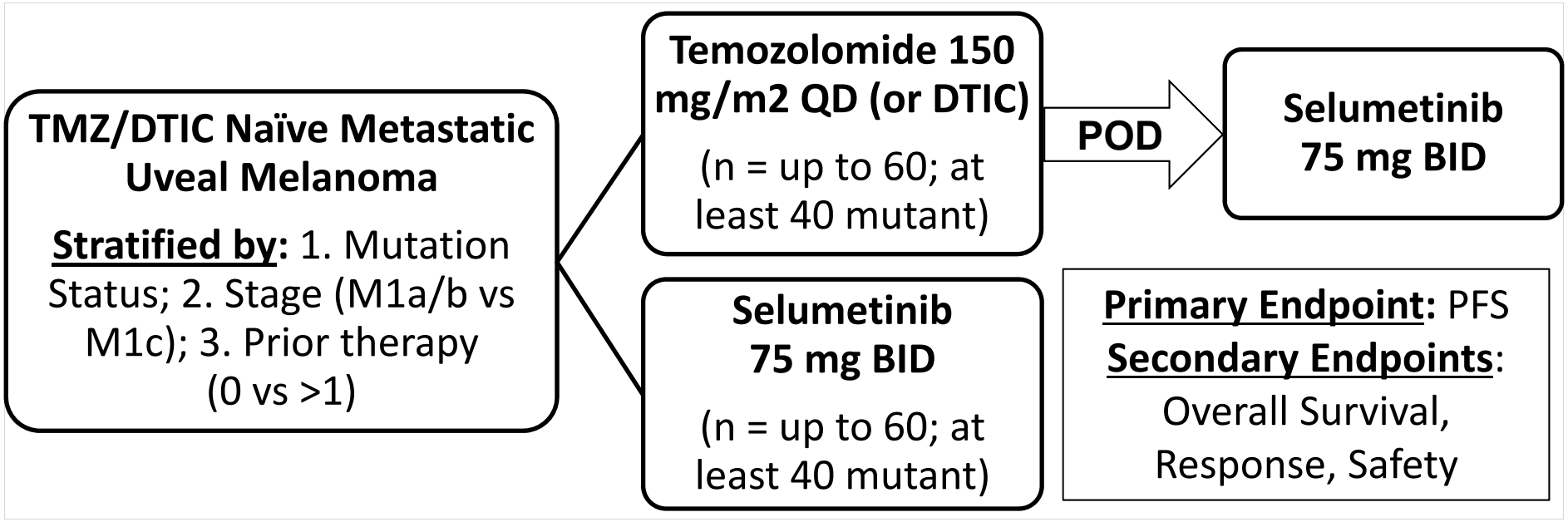
- Gnaq/Gna11 mutations are frequent early oncogenic events in uveal melanoma
- Gnaq/Gna11 encode for members of the q class of G-protein alpha subunits
- Mutations in Gnaq/Gna11 result in activation of the MAPK pathway

Onken et al. *Investigative Ophthalmology and Visual Science*, 2008; Van Raamsdonk *et al. Nature*, 2008; Van Raamsdonk *et al. NEJM*, 2010.

We therefore systematically assessed the efficacy of selumetinib, a non-ATP competitive inhibitor of MEK1/2, in patients with metastatic uveal melanoma

Presented by: RD Carvajal

Study Design



- Radiographic assessments using RECIST 1.1 performed at week 4, week 8, and every 8 weeks subsequently
- Patients treated until progression, intolerable toxicity, or withdrawal of consent

Probability is 80% that this design will detect a treatment difference at a one-sided 10% significance level if the true PFS hazard ratio is 0.68 in the overall population AND 0.6 in the Gnaq/11 mutant population

Presented by: RD Carvajal

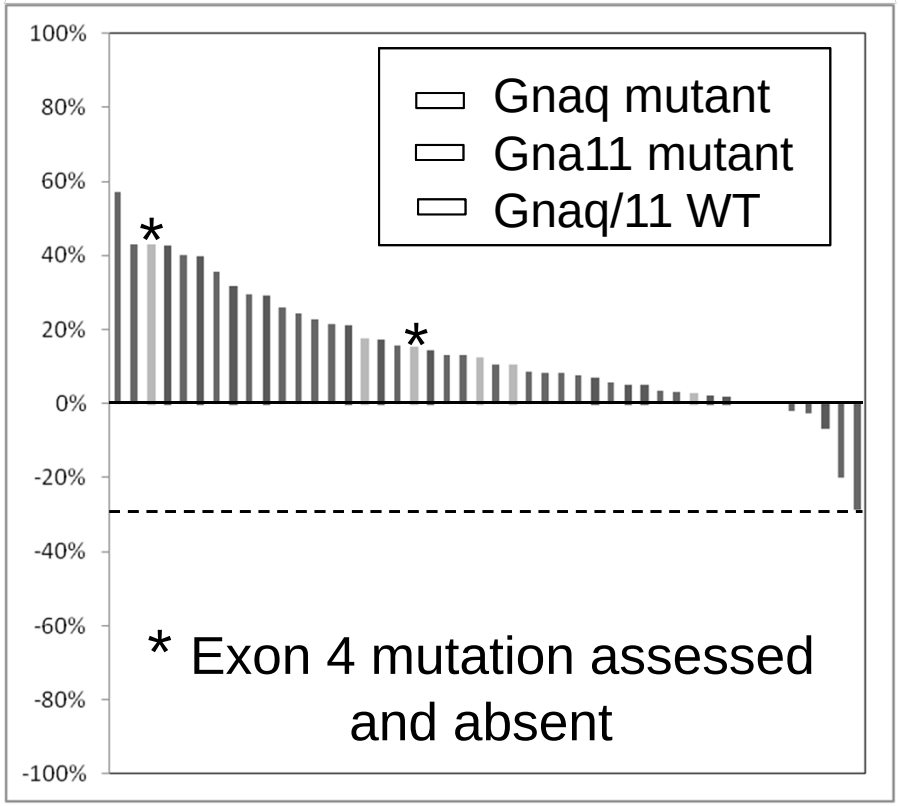
Select Non-Hematologic Toxicities Possibly, Probably or Definitely Related to Therapy Observed in > 5% of Cases

	TMZ/DTIC (n = 49)			Selumetinib (n = 47)		
Toxicity	**Gr 1/2**	**Gr 3**	**Gr 4**	**Gr 1/2**	**Gr 3**	**Gr 4**
Rash	3 (6%)	-	-	40 (85%)	1 (2%)	-
Fatigue	24 (49%)	-	-	28 (60%)	-	-
CPK Elevation	-	-	-	17 (36%)	6 (13%)	-
AST/ALT	6 (12%)	-	-	16 (34%)	7 (15%)	-
Diarrhea	4 (8%)	-	-	19 (40%)	-	-
Edema	1 (2%)	-	-	18 (38%)	1 (2%)	-
Nausea	19 (39%)		-	18 (38%)	-	-
Vomiting	11 (22%)	-	-	11 (23%)	-	-
Pain	5 (10%)	-	-	10 (21%)	-	-
Mucositis	1 (2%)	-	-	6 (13%)	-	-
Dyspnea	-	-	-	7 (8%)	1 (2%)	-
Muscle Weakness	-	-	-	7 (8%)	-	-

Presented by: RD Carvajal

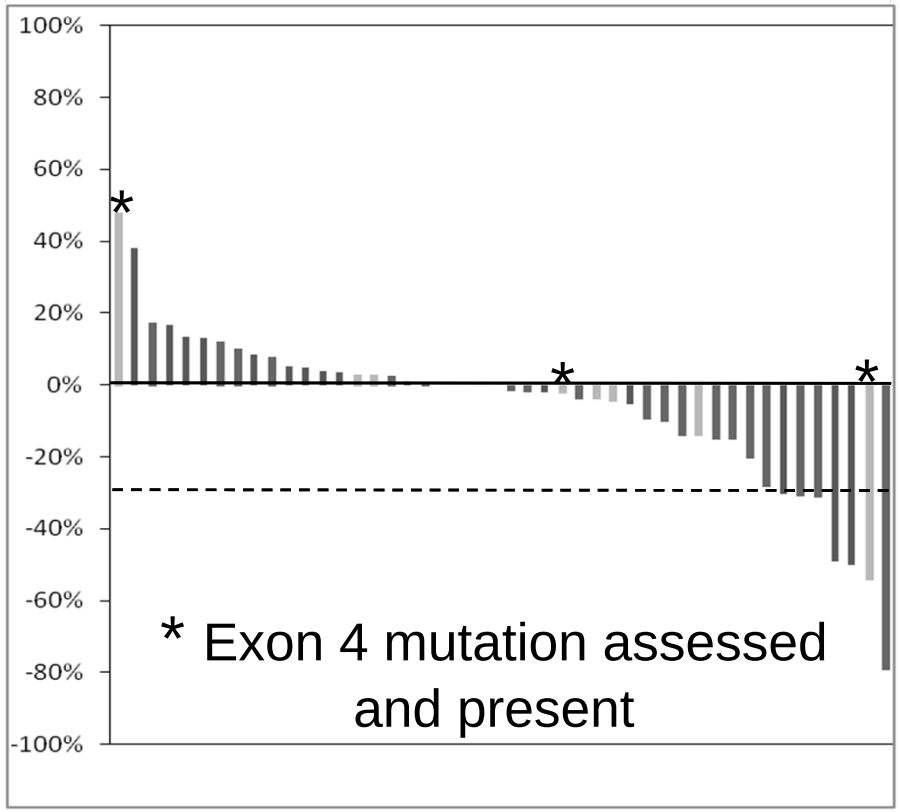
Response Pattern Differs Between Treatment Arms

Temozolomide/DTIC
(n = 46 evaluable for response)



Tumor Regression: 11%
RECIST Response: 0%

Selumetinib
(n = 46 evaluable for response)

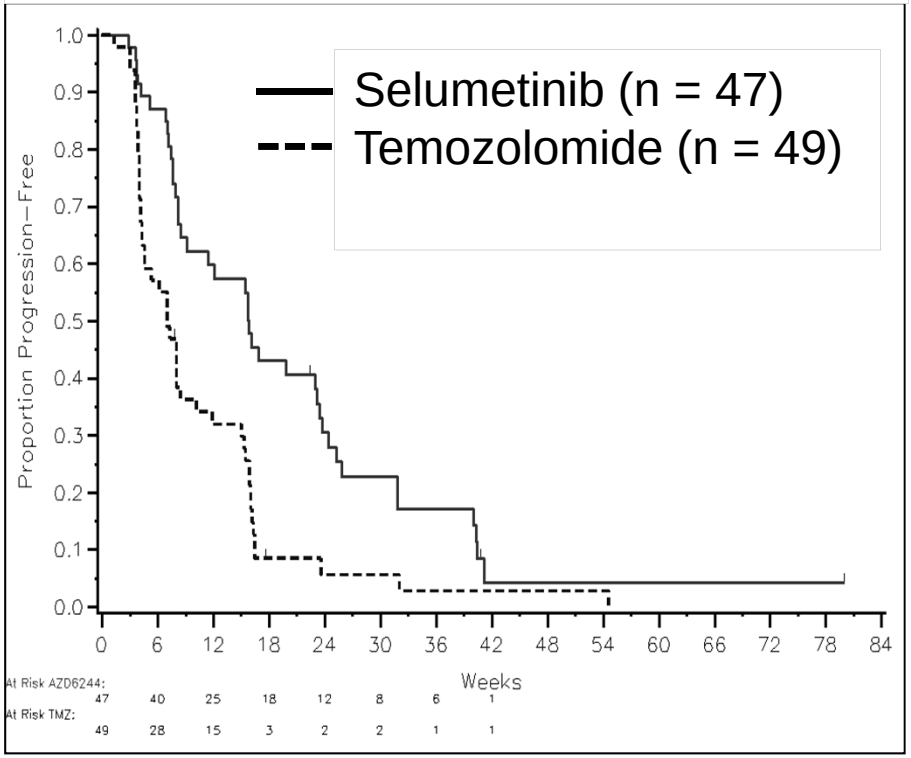


Tumor Regression: 50%
RECIST Response: 15%

Presented by: RD Carvajal

Progression-Free Survival is Improved with Selumetinib in Both the Overall and Mutant Only Populations

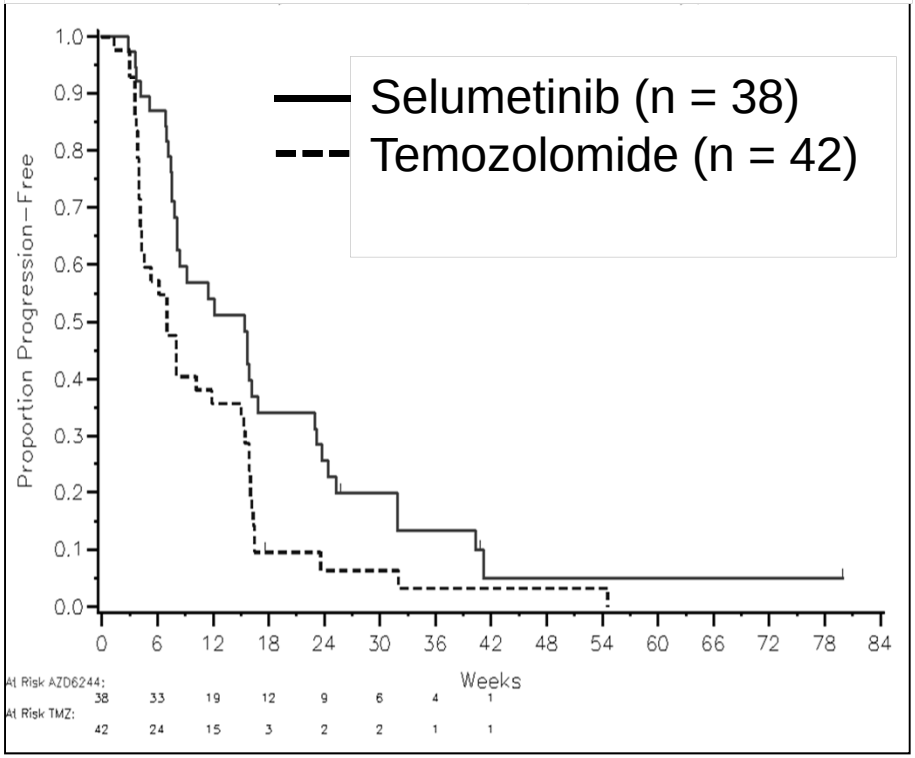
Overall Population



15.9 weeks (95% CI, 8.4 – 23.1) vs
7.0 weeks (95% CI, 4.3 – 8.4)

HR 0.46 (95% CI, .30 - .71)
p = 0.0005

Exon 5 Gq/11 Mutation Positive



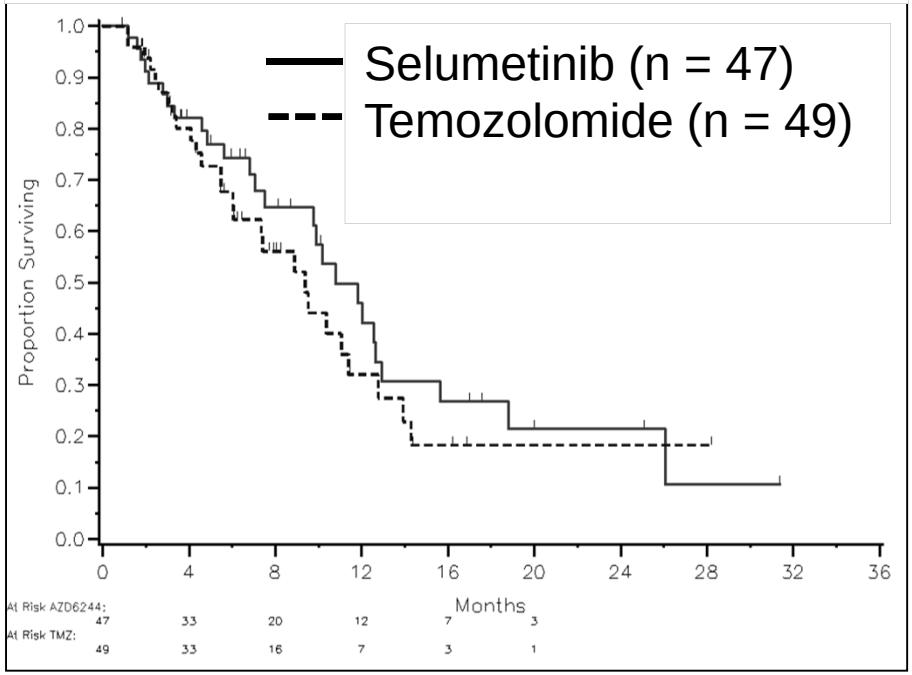
15.4 weeks (95% CI, 8.1 – 16.9) vs
7.0 weeks (95% CI, 4.3 – 11.9)

HR 0.55 (95% CI, .34 - .87)
p = 0.011

Presented by: RD Carvajal

No Significant Effect Upon Survival is Observed

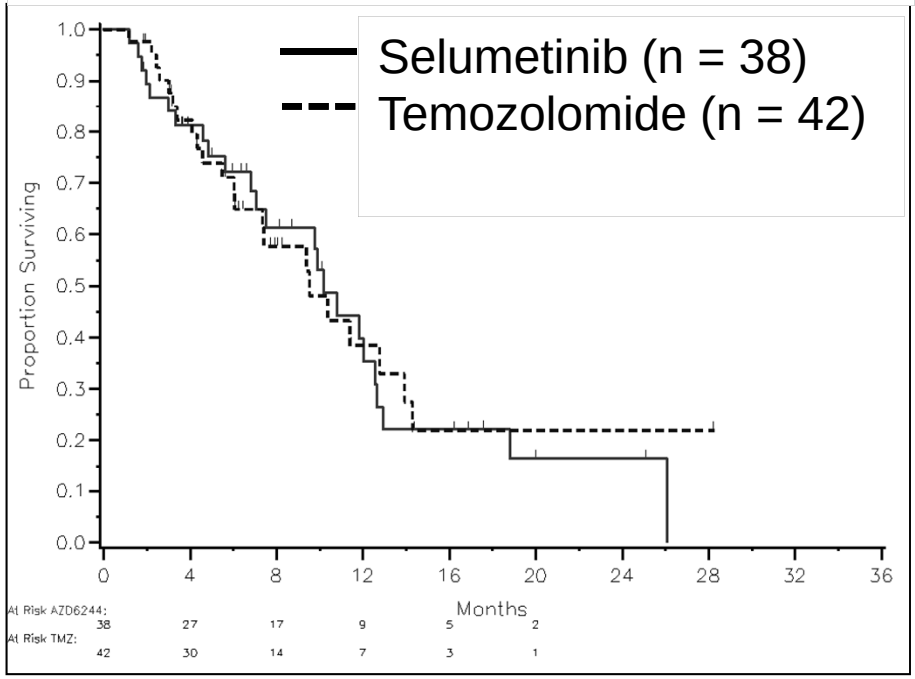
Overall Population



10.8 months (95% CI, 7.5 – 12.9) vs
9.4 months (95% CI, 6.0 – 11.4)

HR 0.79
(95% CI, 0.46 – 1.37)
p = 0.4

Exon 5 Gq/11 Mutation Positive



10.2 months (95% CI, 7.0 – 12.6) vs
9.5 months (95% CI, 6.1 – 13.9)

HR 1.05
(95% CI, 0.59 – 1.88)
p = 0.88

Presented by: RD Carvajal

Conclusions

- This study is the first to demonstrate improved clinical outcome with any systemic therapy in patients with metastatic uveal melanoma

- MEK inhibition with selumetinib results in a median progression-free survival double that achieved with chemotherapy in uveal melanoma (15.9 vs 7 weeks)

- Tumor shrinkage is achieved in 50% patients treated with selumetinib, with 15% achieving a RECIST response

- Patients previously treated with chemotherapy may be less likely to respond to selumetinib

- Selumetinib is a promising therapy for patients with advanced uveal melanoma and provides a platform for the development of new combinatorial therapeutic approaches

Presented by: RD Carvajal

ABSTRACTS FROM STUDENT POSTER PRESENTATIONS

Abstract Submission for 2013 Georgia Society of Clinical Oncology, Atlanta, GA

The Role of IGF-II as a Tumor Marker for Cervical Cancer: Can IGF-II be used to monitor and screen patients specifically for cervical cancer?

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Background: In the U.S. there are over 12,000 new cases of cervical cancer each year and the estimated cost of screening and treating cervical cancer annually is 6 billion dollars. Although the Pap smear is the mainstay of screening and has significantly decreased the number of new cases and deaths from cervical cancer, the test is associated with poor accuracy, a high false negative rate, patient inconvenience, and an inappropriate means of testing in certain cultures. Our clinical observations suggests that there is a need for a more accurate, convenient and non-invasive test for cervical cancer.

Several retrospective studies have shown that IGF-II may play an important role in cervical tumorigenesis by discovery of significant elevations in serum IGF-II levels in patients with cervical cancer as compared to controls. In 2005, Mathur, et al. showed that elevation of IGF-II in the cervical epithelium or in the blood appears so far to be specific to persistent/recurrent cervical cancer and advanced CIN. Their findings led them to believe that serum levels of IGF-II could be confidently used for the early diagnosis of cervical cancer and for monitoring its therapy efficacy.

Objective: The primary objective of this study was to demonstrate that IGF-II is significantly elevated in cervical cancer over the normal published range (450-700 ng/mL), and to determine whether IGF-II is elevated sufficiently to detect HGSIL and cervical cancer as compared to controls. Our second aim was to determine if IGF-II levels return to baseline after successful therapy of cervical cancer and potentially use IGF-II as a tumor marker for diagnosis and treatment surveillance.

Methods: Patients at Georgia Regents University in Augusta, GA were selected sequentially when they met inclusion criteria and agreed to enroll in this prospective cohort study. In this IRB approved protocol, patients were enrolled in one of three groups: 1) Healthy controls, 2) Women with cervical biopsy that showed CIN II or III (true precancerous lesions), or 3) Cervical Cancer. After informed consent was obtained, serum IGF-II was collected from each patient by venipuncture at two different time points, t=0 months and t≥3 months (following treatment with surgery or chemotherapy for CIN II/III and cancer groups). IGF-II levels were measured using ELISA kits at a contract-testing laboratory. Samples were sent to a lab technician and a biostatistician in a blinded fashion. Blinding was not broken until the end of the study by the investigating team, once all blood samples were tested.

All analyses were performed using SAS 9.2. To examine change over time in IGF-II between the 3 groups and to determine the population size required for this study, the following assumptions were made: the alpha level was set at .05; the power was set at .8, .85, and .9; the correlation of IGF-II levels between time points had a subject of .2, .5, and .8; and a standard deviation of 150 and 200 ng/mL was selected. Calculations based on these parameters indicated that a population size of 15-20 patients per group should be recruited. Therefore, 20 patients were chosen for each group.

Baseline demographics and clinical characteristics among the 3 groups were examined for differences using a repeated measures mixed model. Post hoc pair-wise comparisons between the three groups were performed using Bonferroni adjustment to the overall alpha level for the number of comparisons.

Results: Sixty patients were enrolled in the study and underwent serum IGF-II blood draws prior to any intervention. In the control group, the mean serum IGF-II level was 402.3 ng/mL (195-622 ng/mL). The CIN II/III group had a mean value of 432.35 ng/mL (315-651 ng/mL). The mean IGF-II level in the cervical cancer group was 420.3 ng/mL (265-626 ng/mL). Preliminary ANOVA results revealed a p-value of 0.61 when comparing between the three groups. Thus, there was not a statistically significant difference between the groups, and we were unable to show in this prospective study that IGF-II plays a significant role in high grade cervical lesions and cervical cancer.

Conclusions: The basis of this study was to look at a novel method for detecting cervical cancer and potentially use that same marker for monitoring response to therapy. However, despite an adequate study design, there was no significant difference in IGF-II serum levels among controls, patients with high grade cervical lesions and patients with cervical cancer. As a consequence of these initial findings and financial limitations, we did not pursue the second part of the trial, which involved submitting samples for serum levels of IGF-II at t>3 months. Instead, these samples have been saved for future prospective studies involving other tumor markers that may play a role in cervical cancer. In conclusion, we accept the null hypothesis that there is no difference in IGF-II levels in the serum of women with a normal Pap smear, women with CIN II/III, and women with carcinoma of the cervix.

AGUS Pap Smear as a Marker for a GI Malignancy: A Case Report & Literature Review

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Abstract

Introduction: A Pap smear demonstrating atypical glandular cells of undetermined significance (AGUS) is associated with pre-malignant or malignant disease of the cervix in 30-35% of cases. However, in rare instances it can be a marker for extra cervical malignant disease of the uterus, ovary, fallopian tube or primary peritoneal cancers. We present the first reported case of an AGUS pap smear as the first trigger to diagnose an asymptomatic patient with appendiceal cancer. Furthermore, a literature review revealed only 5 other cases of primary GI malignancies diagnosed by an AGUS pap smear.

Case description: A 52-year-old asymptomatic female, with a history of normal pap smears, presented for a routine annual gynecologic exam. Physical examination was remarkable for cervical thickening and an enlarged, immobile uterus. The Pap smear revealed atypical glandular cells of undetermined significance (AGUS). Follow up colposcopic examination demonstrated a punctuated ecto-cervical lesion. Biopsy of the lesion, as well as an endo-cervical curettage, showed a carcinoma with signet ring cells beneath the cervical mucosa. Subsequent endometrial biopsy revealed clusters of atypical signet ring cells, within apparent vascular and lymphatic spaces, and dysynchronous endometrium with proliferative glands. These results triggered a colonoscopy with biopsy of an invasive lesion at the cecum, near the appendiceal ostium showing identical poorly differentiated adenocarcinoma with signet ring cells. The patient underwent exploratory laparotomy, right hemi-colectomy with ileal transverse colostomy, lymphadenectomy, and total abdominal hysterectomy with bilateral salpingo-oophorectomy. Histologic examination revealed an appendix with mixed adenocarcinoid tumor, with involvement of the cecum and adjacent terminal ileum, and extension into the periappendiceal fat. The uterus consisted of multiple areas of metastatic adenocarcinoid in the myometrium and cervix, with vascular invasion. 9 of 27 lymph nodes were positive for metastatic carcinoma. The patient was treated with 5-Fluorouracil and Leukovorin. A post-chemotherapy CT scan of the abdomen and pelvis was negative for evidence of recurrence.

Discussion: The case illustrates that metastatic disease of a GI malignancy may present as an abnormal Pap smear (AGUS) in an asymptomatic patient. The incidental finding of AGUS on Pap smear imparts a significant diagnostic challenge. In the atypical presentation, it is important to consider metastatic disease from extra genital sites and tailor the diagnostic course accordingly. A Medline literature search demonstrates the rarity of such occurrences as illustrated by the following table.

Primary Malignancy	Pap Smear/Cervical Biopsy	Signs and Symptoms
Colon adenocarcinoma [10]	Adenocarcinoma/adenocarcinoma	None
Colon carcinoma [11]	Pap: AGUS	Unknown
Colon carcinoma [12]	Pap: Adenocarcinoma	Unknown
Gastric carcinoma [13]	Signet ring cells/signet ring cell carcinoma	Abdominal distention, weight loss, anorexia, postprandial fullness
Gastric carcinoma [14]	Signet ring cells/negative biopsy	Ascites
Gastric carcinoma [15]	Pap: Adenocarcinoma	Epigastric pain, postprandial vomiting
Gallbladder adenocarcinoma [16]	Adenocarcinoma/adenocarcinoma	Pain in left lumbar area and left flank, bloating, postprandial burning, anorexia, abdominal discomfort

This report demonstrates the first appendiceal carcinoid tumor diagnosed by a AGUS pap smear in an asymptomatic patient.

Outcomes of hematopoietic stem cell transplant recipients admitted to the medical intensive care unit

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Background: The number of allogeneic hematopoietic stem cell transplants (HSCT) from unrelated donors (URD) surpassed the number of allogeneic transplants from related donors after 2006, mainly due to the growth of URD databases, improvements in URD transplant and supportive care. As a result, complications related to URD such as organ failure and infectious complications are seen in higher numbers. Data related to the intensive care unit (ICU) admissions in HSCT patients and their prognosis is infrequently reported during this period, especially in view of the recent technological advances in the field of critical care. We have evaluated the predictors of mortality in HSCT recipients admitted to the ICU.

Methods: We have retrospectively evaluated 34 HSCT patients admitted to ICU among the 390 HSCTs performed from March 2011 until July 2012. 22 patients received mechanical ventilation (MV) or vasopressor support and were analyzed seperately. All previously defined predictors of mortality were evaluated. SPSS version 20 was used for statistical analysis.

Results: 41% of patients were admitted for respiratory failure and 23.5% for sepsis. Median age of the patients was 55.5 (range: 27-76). Median length of ICU stay was 7 days (0-42) and median APACHE II score was 20 (9-39). Major underlying hematological malignancies were AML/MDS (29%) and myeloma (24%). Graft source was peripheral blood in 97% of patients; and close to 40% of patients received URD transplant. Predictors for day 30 mortality on univariate analysis among all patients were APACHE II score ≥26 (p=0.05). Predictors for day 60 mortality were APACHE II score ≥31 (p=0.001) and multiorgan failure (p=0.009). Among the patients that were receiving MV or vasopressors, APACHE II score ≥31 is the only significant predictor of mortality (p=0.011). On multivariate analysis, APACHE II score ≥31 at day 30 hazards ratio (HR) 3.777 (95%CI 1.041-13.69; p=0.043) and at day 60 HR 3.789 (95%CI 1.07-13.45; p=0.039) is a significant predictor of mortality.

Conclusions: 9% of HSCT patients were admitted to ICU. 30 day and 60 day mortality rates are 47% and 62% among all patients; 54% and 68% among MV patients or receiving vasopressors. Significant predictors identified on multivariate analyses were APACHE II score ≥31 at day 30 and day 60. Future studies with larger patient samples and longer follow up are required for further understanding of prognosis in these patients.

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