LBA9000 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

AVAST-M: Adjuvant bevacizumab as treatment for melanoma patients at high risk of recurrence.

Philippa Corrie, Andrea Marshall, Madusha Goonewardena, Janet A. Dunn, Mark R. Middleton, Paul D. Nathan, Martin Eric Gore, Neville Davidson, Steve Nicholson, Charles G. Kelly, Maria Marples, Sarah Danson, Ernest Marshall, Stephen Houston, Ruth E. Board, Ashita Marie Waterston, Jenny Nobes, Mark Harries, Jim Barber, Paul Lorigan; Oncology Centre, Addenbrooke's Hospital, Cambridge, United Kingdom; Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom; Cambridge Clinical Trials Unit, Cancer Theme, Addenbrooke's Hospital, Cambridge, United Kingdom; Churchill Hospital Cancer Center, Oxford, United Kingdom; Mount Vernon Cancer Centre, Northwood, United Kingdom; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Oncology Research, Broomfield Hospital, Chelmsford, United Kingdom; Oncology Department, Leicester Royal Infirmary, Leicester, United Kingdom; Sir Bobby Robson Cancer Trials Research Centre, Freeman Hospital, Newcastle upon Tyne, United Kingdom; Cancer Research, St James's University Hospital, Leeds, United Kingdom; Cancer Research Centre, Weston Park Hospital, Sheffield, United Kingdom; Cancer & Palliative Care, St. Helens Hospital, St Helens, United Kingdom; Oncology Department, Royal Surrey County Hospital, Guildford, United Kingdom; Oncology Department, Royal Preston Hospital, Preston, United Kingdom; Clinical Trials Unit, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Clinical Oncology, Norfolk & Norwich University Hospital, Norwich, United Kingdom; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; Velindre Cancer Centre, Cardiff, United Kingdom; Department of Medical Oncology, Christie Hospital, Withington, Manchester, United Kingdom

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9001 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Adjuvant radiotherapy after lymphadenectomy in melanoma patients: Final results of an intergroup randomized trial (ANZMTG 0.1.02/TROG 02.01).

Michael A. Henderson, Bryan Burmeister, Jill Ainslie, Richard Fisher, Julianna Di Iulio, Bernard Mark Smithers, Angela Hong, Kerwin F. Shannon, Richard A Scolyer, Scott Carruthers, Brendon J Coventry, Scott Babington, Joao Duprat, Harald J. Hoekstra, John F Thompson; Peter MacCallum Cancer Center, Melbourne, Australia; Princess Alexandra Hospital / University of Queensland, Woolloongabba, Australia; Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, Australia; Center for Biostatistics and Clinical Trials Peter MacCallum Cancer Center, Melbourne, Australia; Princess Alexandra Hospital, Woolloongabba, Australia; Royal Prince Alfred Hospital, Camperdown, Australia; Melanoma Institute of Australia, Royal Prince Alfred Hospital, Sydney, Australia; Melanoma Institute Australia, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia; Royal Adelaide Hospital, Adelaide, Australia; Christchurch Hospital, Christchurch, New Zealand; Hospital do Cancer, Sao Paulo, Brazil; University Medical Center Groningen, Groningen, Netherlands

Background: The role of adjuvant radiotherapy following lymphadenectomy in melanoma patients identified as at high risk for further recurrence has been controversial. This final report of a multicenter randomized trial updates survival and lymph node field (LNF) control, and reports long term treatment toxicity, lymphedema and quality of life (QOL) (Lancet Oncol 2012;13:589-97). **Methods:** Patients at high risk of LNF relapse (≥1 parotid, ≥2 cervical or axillary or ≥3 groin positive nodes; or extra-nodal spread of tumour; or minimum metastatic node diameter of 3cm (neck or axilla) or 4cm (groin)) received adjuvant radiotherapy (ART) (48Gy in 20 fractions) or observation (OBS). LNF relapse, as a 1st relapse, was the primary endpoint; morbidity, QOL, patterns of relapse, disease free and overall survival were secondary endpoints. A target sample size of 250 enabled detection of a difference in 3 year relapse rates of 30% and 15% to be detected (2-sided logrank test, power of 80%). **Results:** 250 patients from 16 centres were randomized from Mar 02 to Sept 07 (123 ART; 127 OBS) with 217 fully eligible (109 ART, 108 OBS). Mean follow-up 73 months (range 21–116). LNF recurrence was reduced in the ART arm (HR=0.52 (0.31-0.88) p=0.023) but there was no difference in survival (HR=1.13 (0.82 – 1.55) p =0.21). QOL was assessed by comparison of area under the curve from baseline to 5 years (or recurrence) with the FACT-G tool using both total score and the 4 major domains (physical, social, emotional and functional wellbeing), no difference. Regional symptoms (standardised questionnaire) were higher in the ART arm (p=0.035). Limb volumes were higher in the ART arm (leg 7.3% difference p=0.014, arm 3.4% p=0.25). Grade 2-4 RT toxicity was common for head + neck: skin (33%); axilla: skin (44%), subcutaneous tissue (41%); Groin: skin (46%), subcutaneous tissue (67%), other (38%). **Conclusions:** RT reduced the risk of LNF relapse by 52% but there was no impact on survival. In the ART arm loco-regional symptoms were worse, limb volumes were somewhat increased and Grade 2 - 4 long term RT toxicity was relatively common. However QOL as assessed by a validated tool (FACT-G) was similar in both groups. Clinical trial information: NCT00287196.

9002 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Next-generation sequencing of genomic and cDNA to identify a high frequency of kinase fusions involving ROS1, ALK, RET, NTRK1, and BRAF in Spitz tumors.

Phil Stephens, Thomas Wiesner, Jie He, Roman Yelensky, Rosaura Esteve-Puig, Geoff Otto, Michael F. Berger, Doron Lipson, Kristina Brennan, Vincent A. Miller, Maureen T. Cronin, Boris C. Bastian; Foundation Medicine, Inc., Cambridge, MA; Human Oncology & Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY; Foundation Medicine, Cambridge, MA; University of California, San Francisco, San Francisco, CA; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Spitz tumors are melanocytic neoplasms with characteristic morphologic features that can overlap with melanoma. Predicting biologic behavior, which can range from an indolent disease to metastasis confined to regional lymph nodes and infrequent incidences of widespread metastatic disease with lethal outcome, is unreliable based on histopathological criteria and the genetic underpinnings of the disease as a whole are poorly understood. **Methods:** Genomic DNA and total RNA was isolated from 40 microns of FFPE sections from 20 benign Spitz nevi and 8 atypical Spitz tumors (with morphological features inconsistent with *HRAS* or *BRAF*/*BAP1* mutations) in a CLIA-certified lab (Foundation Medicine). DNA sequencing was performed for 3230 exons of 182 cancer-related genes plus 37 introns of 14 genes commonly fused on indexed hybridization-captured libraries to an average unique coverage of 997x, with 99.96% of exons being sequenced at $\geq$100x coverage. RNA sequencing was performed on indexed libraries captured using the cDNA Kinome hybridization kit (Agilent) generating $>$50,000,000 unique pairs per specimen. **Results:** Only a single case harbored a point mutation in a gene known to be recurrently mutated in melanocytic neoplasms, *HRAS* Q61L and no known alterations were found in *BRAF*, *NRAS*, *KIT*, *GNAQ* or *GNA11*. Remarkably, genomic rearrangements were observed in 19/28 (68%) of cases. The rearrangements fused the intact kinase domains of *ROS1* (36%), *ALK* (14%), *RET* (7%), *NTRK1* (7%) and *BRAF* (4%) to a wide range of predominantly novel 5' partners including PWWP2A, PPFIBP1, ERC1, MYO5A, CLIP1, HLA-A, ZCCHC8, DCNT1, LMNA and CEP89. These gene rearrangements, which were all expressed, formed constitutively activated chimeric oncogenes. All fusions occurred in a mutually exclusive pattern and were more common in younger patients compared to patients whose tumors did not harbor fusions (median age 14 versus 24 years, $p=0.02$). **Conclusions:** Next generation sequencing identified gene fusions in two thirds of Spitz tumors which are likely to be useful as diagnostic markers that may also serve as therapeutic targets for the rare subset of these tumors that metastasize.

CRA9003 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

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

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

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9004 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Phase II double-blind, randomized study of selumetinib (SEL) plus dacarbazine (DTIC) versus placebo (PBO) plus DTIC as first-line treatment for advanced *BRAF*-mutant cutaneous or unknown primary melanoma.

Mark R. Middleton, Reinhard Dummer, Ralf Gutzmer, Paul Lorigan, Kevin Kim, Marta Nyakas, Ana Maria Arance, Gabriella Liszkay, Dirk Schadendorf, Mireille Veronique Cantarini, Stuart Spencer, Caroline Robert; Oxford University Hospitals NHS Trust, Oxford, United Kingdom; University Hospital Zurich, Dermatology, Zurich, Switzerland; Medizinische Hochschule, Hannover, Germany; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; The University of Texas MD Anderson Cancer Center, Houston, TX; Rikshospitalet-Radiumhospitalet HF, Oslo, Norway; Hospital Clínic, Barcelona, Spain; Országos Onkológiai Intézet, Budapest, Hungary; Universitätsklinikum Essen, Essen, Germany; AstraZeneca UK Ltd, Macclesfield, United Kingdom; Institut Gustave Roussy, Paris, France

Background: *BRAF* mutations play an oncogenic role in melanomas. Selumetinib (AZD6244, ARRY-142886) inhibits MEK1/2 downstream of B-Raf and may have an additive effect to chemotherapy. We prospectively evaluated SEL + DTIC vs PBO + DTIC in patients with stage III-IV *BRAF* mutation-positive advanced cutaneous or unknown primary melanoma (NCT00936221). **Methods:** Eligible patients (pts) received iv DTIC 1000 mg/m^2, and po SEL 75 mg or matched PBO bd as first-line treatment. The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety and tolerability. **Results:** A total of 385 pts were screened across 44 centers; 91 patients were randomized (SEL + DTIC, 45; PBO + DTIC, 46). One pt from each group did not receive the randomized treatment. Baseline characteristics were balanced between the two groups, with the exception of histology, gender and previous medications. At data cut-off, 66 deaths had occurred (73% maturity) and median follow-up was 12.3 mo. OS was longer for SEL + DTIC vs PBO + DTIC (median 13.9 vs 10.5 mo), but this did not meet statistical significance (HR 0.93; 80% CI 0.67, 1.28; 1-sided p=0.3873). PFS was significantly improved for SEL + DTIC vs PBO + DTIC, median 5.6 vs 3.0 mo (HR 0.63; 80% CI 0.47, 0.84; 1-sided p=0.021). ORR was 40% with SEL + DTIC vs 26% with PBO + DTIC. Most frequent adverse events (AEs) observed with SEL + DTIC were: nausea (64%), dermatitis acneiform (52%), diarrhea (48%), vomiting (48%), and peripheral edema (43%). AEs that led to hospitalization were higher for SEL + DTIC vs PBO + DTIC (36 vs 13%), and were mostly infections and gastrointestinal disorders. The incidence of grade ≥3 AEs (68 vs 42%), serious AEs (50 vs 18%) and discontinuation of the randomized treatment due to AEs were higher for SEL + DTIC vs PBO + DTIC (16 vs 4%). **Conclusions:** Clinical activity was observed in patients with *BRAF* mutation-positive melanoma treated with SEL + DTIC, reflected by a nonsignificant improvement in OS and a significant benefit in PFS. Tolerability of this combination was generally consistent with the monotherapy safety profiles. Clinical trial information: NCT00936221.

9005 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

BRAF inhibitor (BRAFi) dabrafenib in combination with the MEK1/2 inhibitor (MEKi) trametinib in BRAFi-naive and BRAFi-resistant patients (pts) with BRAF mutation-positive metastatic melanoma (MM).

Jeffrey Alan Sosman, Adil Daud, Jeffrey S. Weber, Kevin Kim, Richard Kefford, Keith Flaherty, Jeffrey R. Infante, Omid Hamid, Jonathan S. Cebon, Lynn Mara Schuchter, Robert R. McWilliams, Mario Sznol, William Howard Sharfman, Alain Patrick Algazi, Karl D. Lewis, Shonda M Little, Peng Sun, Georgina Long, Kiran Patel, Rene Gonzalez; Vanderbilt University Medical Center, Nashville, TN; University of California, San Francisco, San Francisco, CA; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; Westmead Hospital and Melanoma Institute Australia, Westmead, Australia; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; The Angeles Clinic and Research Institute, Los Angeles, CA; Ludwig Institute for Cancer Research, Melbourne, Australia; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Mayo Clinic, Rochester, MN; Yale University, New Haven, CT; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; University of Colorado Cancer Center, Aurora, CO; GlaxoSmithKline, Collegeville, PA; University of Sydney, Sydney, Australia; UCHSC, Anschultz Cancer Pavilion, Aurora, CO

Background: Dual inhibition of the MAP kinase (MAPK) pathway with dabrafenib (D) and trametinib (T) in combination has demonstrated clinical benefit compared to D alone in a randomized Phase II trial in V600 BRAF-mutant MM pts, thus delaying the development of BRAFi resistance. Little is known about the efficacy of D + T after BRAFi resistance has been acquired. This analysis evaluates the ability of D + T combination to treat acquired resistance compared to the D + T combination as first-line treatment. **Methods:** These data from a phase I/II study include 1. BRAFi-resistant group: pts who received 150/2 D+T in Part B (n=26) and Part C (n=43) following progression on BRAFi monotherapy (mono); 2. BRAFi-naïve group: pts who received initial 150/2 D+T in Part B (n=24) and Part C (n=54). **Results:** Baseline characteristics (ECOG PS, M staging, LDH) were similar across all groups.In the Part B BRAFi-resistant group, 93% of pts previously received D or vemurafenib and all pts received D prior to D+T in Part C. In BRAFi-resistant group, prior best response of CR/PR (38%, 56%), SD (35%, 27%), PD (27%, 7%) was observed in Parts B and C respectively. In BRAFi-resistant group, the ORR and PFS with D+T was lower than initial D+T in BRAFi-naive group. Median duration of response (DoR) in BRAFi-resistant group cannot be calculated due to small no. of pts responding. Median DoR for BRAFi-naïve pts was 11.3 mo and 10.5 mo in Parts B and C respectively. In Part C, the 12-mo overall survival rates in BRAFi-naïve (150/2) pts was 79% vs 70% for pts initially on D mono, despite 80% pts crossing over to D+T combination. **Conclusions:** The clinical activity for 150/2 D+T combination is consistently superior in BRAFi-naive group vs BRAFi-resistant group in both Parts B and C. Dual MAPK blockade can delay clinical resistance to BRAF inhibition. However, once BRAFi resistance has occurred, the combination of BRAFi + MEKi is far less effective. Clinical trial information: NCT01072175.

	BRAFi resistant		BRAFi naive	
Cohort	**Part B**	**Part C**	**Part B**	**Part C**
Treatment group	150/2 combination N=26	Mono X-over 150/2 combination N=43	150/2 combination N=24	150/2 combination N=54
PFS, median, months	3.6	3.6	10.8	9.4
ORR, %	15%	9%	63%	76%

CRA9006^ **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

Survival and long-term follow-up of safety and response in patients (pts) with advanced melanoma (MEL) in a phase I trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538).

Mario Sznol, Harriet M. Kluger, F. Stephen Hodi, David F. McDermott, Richard D. Carvajal, Donald P. Lawrence, Suzanne Louise Topalian, Michael B. Atkins, John D. Powderly, William Howard Sharfman, Igor Puzanov, David C. Smith, Jon M. Wigginton, Georgia Kollia, Ashok Kumar Gupta, Jeffrey Alan Sosman; Yale Cancer Center, New Haven, CT; Yale University, New Haven, CT; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; Massachusetts General Hospital Cancer Center, Boston, MA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC; Carolina BioOncology Institute, Huntersville, NC; Vanderbilt University Medical Center, Nashville, TN; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Bristol-Myers Squibb, Princeton, NJ

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CRA9007 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

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

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

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LBA9008 **Oral Abstract Session, Sat, 1:15 PM-4:15 PM**

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.

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

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9009 **Clinical Science Symposium, Sun, 9:45 AM-11:15 AM**

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

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.

9010 **Clinical Science Symposium, Sun, 9:45 AM-11:15 AM**

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

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.

9011 **Clinical Science Symposium, Sun, 9:45 AM-11:15 AM**

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

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.

9012^ **Clinical Science Symposium, Sun, 9:45 AM-11:15 AM**

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

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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.

Cohort	Ipilimumab (mg/kg) + nivolumab (mg/kg)	n[a]	CR[b] (n)	PR[b] (n)	ORR (%) [95% CI]	≥80% Tumor reduction at 12 wk (%)
1	3 + 0.3	14	1	2	21 [5-51]	4/14 (29)
2	3 + 1	17	3	5	47 [23-72]	7/17 (41)
3	3 + 3	6	0	3	50 [12-88]	0/6 (0)
2a	1 + 3	12			Ongoing	
6	Prior + 1	14			Ongoing	
7	Prior + 3	6			Ongoing	

[a]Total treated; [b]mWHO criteria.

9013 Poster Discussion Session (Board #1), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM).

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Background: Dabrafenib is a selective BRAF inhibitor with demonstrated efficacy in BRAF V600E-positive mutation in MM. The primary analysis of BREAK-3 (NCT01227889) compared progression-free survival (PFS) in patients (pts) with BRAF V600E-positive mutation MM treated with dabrafenib or DTIC. **Methods:** Median PFS for dabrafenib of 5.1 months (mo) and study methods were previously described (Hauschild A, et al. *Lancet*. 2012,380:358–365). Independent review ended at the primary analysis. PFS was updated in Jun 2012 at median follow-up of 10.5 mo for dabrafenib (67% of PFS events), and 9.9 mo for DTIC. Median overall survival (OS) was not reached, so another analysis of OS and safety was performed with data as of Dec 2012, at which time the median follow-up was 15.2 (dabrafenib) and 12.7 (DTIC) mo. PFS of subjects who crossed over was also evaluated at that time. **Results:** PFS hazard ratio was 0.37 [95% CI; 0.23, 0.57]; median PFS was 6.9 mo dabrafenib and 2.7 mo DTIC. In Dec 2012, 36/63 DTIC pts crossed over; median PFS was 4.3 [95% CI; 4.1, 6.1] mos. OS is presented in the Table.The four most common adverse events (AE) on the dabrafenib arm were hyperkeratosis (39%), headache (35%), arthralgia (35%), and pyrexia (32%). Serious AEs ≥ 5% on the dabrafenib arm included cutaneous squamous cell carcinoma/keratoacanthoma (10%) and pyrexia (5%). **Conclusions:** Longer follow-up confirms the benefits of dabrafenib on PFS and response rate. Median OS in the dabrafenib arm was over 18 mo and over 15 mo in the DTIC arm. OS results are confounded by crossover of DTIC pts to dabrafenib and likely by subsequent therapy after progression. The effects of subsequent therapy results will be investigated. The safety profile had no significant changes. Clinical trial information: NCT01227889.

		25 Jun 2012		18 Dec 2012	
		Dabrafenib	DTIC	Dabrafenib	DTIC
OS	# Deaths	55/187 (29%)	21/63 (33%)	78/187 (42%)	28/63 (44%)
	Median	NR	NR	18.2	15.6
	[95% CI]	[NR, NR]	[11.3, NR]	[16.6, NR]	[12.7, NR]
	HR	0.75		0.76	
	[95% CI]	[0.44, 1.29]		[0.48, 1.21]	

NR = not reached. DTIC patients were not censored at crossover.

9014 Poster Discussion Session (Board #2), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Coexistence of multiple escape mechanisms in a $BRAF^{V600E}$-mutated cutaneous melanoma treated with vemurafenib.

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Background: Mechanisms of acquired resistance to vemurafenib are the subject of intense research. Here we report, for the first time, two coexisting yet mutually exclusive mechanisms of escape in a melanoma patient who presented an excellent clinical response following reintroduction of vemurafenib. **Methods:** To investigate the mechanisms of resistance to vemurafenib, we performed whole-exome sequencing using the Illumina technology of a pre-treatment paraffin-embedded lymph node metastasis (Pre) and of two progressing subcutaneous snap-frozen metastases of the right arm (PV1 and PV2). The tumor samples, along with germline controls, were sequenced at high coverage (mean range 268x-356x). **Results:** We identified 107 exonic somatic Single Nucleotide Variants (SNVs) in Pre, 139 SNVs in PV1, and 127 SNVs in PV2, generating a set of 202 different SNVs, 82 of which were common to all 3 samples. The non-synonymous to synonymous ratios were higher for PV1 (1.82) than for PV2 (1.46), and lower for Pre (1.31). C>T transitions, largely predominated in the samples, indicating light-induced damage. Two independent NRAS escape mutations (Q61K and Q61R) where observed in PV1, whereas appearance of a BRAF splice variant (lack of exon 4-10) was present in PV2. Most importantly, these 2 escape mechanisms were mutually exclusive, i.e. no BRAF splice variant was observed by PCR in PV1 and no NRAS mutation found in PV2. **Conclusions:** Our results clearly demonstrate that multiple molecular escape mechanisms can be both coexistent and mutually exclusive. These findings have clinical implications: firstly, local treatment of isolated progressing lesions and continuation of vemurafenib could be supported by the fact that the resistance mechanisms are not necessarily shared. This approach is currently being tested within clinical trials with preliminary results that seem to support this hypothesis. Secondly, the coexistence of divergent escapes within the same patient strongly argues that single biopsy analysis at progression might not reflect the molecular complexity of tumor progression, and therefore might not be sufficient to guide selection of second-line optimal combination therapy.

9015 Poster Discussion Session (Board #3), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Whole exome and whole transcriptome sequencing in melanoma patients to identify mechanisms of resistance to combined RAF/MEK inhibition.

Nikhil Wagle, Eliezer Mendel Van Allen, Dennie T. Frederick, Zachary A. Cooper, Deborah Norman Farlow, Daniel Treacy, Eva M. Goetz, Cory M. Johannessen, Scott L. Carter, Amaro Taylor-Weiner, Eran Hodis, Donald P. Lawrence, Ryan J. Sullivan, Gad Getz, Stacey B. Gabriel, Keith Flaherty, Jennifer Ann Wargo, Levi A. Garraway; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; Broad Institute, Cambridge, MA

Background: The RAF inhibitors vemurafenib and dabrafenib (D) and the MEK inhibitor trametinib (T) improve survival as monotherapies in BRAF-mutant melanoma. Since clinical mechanisms of resistance (MoR) result in MAPK pathway reactivation, recent efforts have focused on combined targeting of RAF and MEK. The combination of D and T (D/T) increased progression-free survival and response rate compared with D alone (Flaherty et al, NEJM, 2012). The MoR to this combination remain unknown. **Methods:** To look for clinical MoR to combined RAF/MEK inhibition, we performed whole exome (WES) and whole transcriptome sequencing (RNASeq) on tumors from 4 patients (pts) with acquired resistance and 1 pt with intrinsic resistance to D/T. Pre-treatment and post-resistance tumors from all pts were analyzed for point mutations, insertions/deletions, copy number alterations, alternatively spliced transcripts, rearrangements, and expression changes. **Results:** In 2 of 4 pts with acquired resistance, WES identified mutations in MEK1 and MEK2 that were undetectable in the pre-treatment tumors. In the 3rd pt, RNASeq identified an alternatively spliced isoform of BRAF lacking exons 2-10, also undetectable in the pre-treatment tumor. In the 4th pt, no obvious MoR were seen, though multiple alterations were enriched in the post-resistance tumor. The pt with intrinsic resistance had several alterations in genes that conferred resistance to RAF/MEK inhibition when overexpressed in BRAF-mutant cell lines. Integration of WES and RNASeq data also identified several co-existing alterations that may synergize to increase resistance. **Conclusions:** Analysis of combined WES and RNASeq data from pt samples provides a more complete picture of clinical MoR to MAPK-targeted therapy. Post-resistance tumors from 3 of 4 pts with acquired resistance to D/T had alterations in MAPK genes not detectable in the pre-treatment tumors, suggesting that resistance involves reactivation of the MAPK pathway despite combined RAF/MEK inhibition. Alternative dosing of current agents, more potent RAF/MEK inhibitors, and/or inhibition of the downstream kinase ERK may be needed for durable control of BRAF-mutant melanoma.

9016 Poster Discussion Session (Board #4), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Comparison of BRAF inhibitor (BRAFi)-induced cutaneous squamous cell carcinoma (cuSCC) and secondary malignancies in BRAF mutation-positive metastatic melanoma (MM) patients (pts) treated with dabrafenib (D) as monotherapy or in combination with MEK1/2 inhibitor (MEKi) trametinib (T).

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Background: The MAP kinase (MAPK) pathway is of critical importance for keratinocyte proliferation and maturation and is essential for epidermal homeostasis. Occurrence of hyperproliferative skin lesions including keratoacanthomas (KA) and cuSCC are considered a class effect of BRAFi [Anforth 2012, Chu 2012, Mattei 2012]. These effects, as well as promotion of pre-existing RAS-driven malignancies, may be caused by paradoxical activation of the MAPK pathway downstream of BRAF in wild-type BRAF cells. As MEK inhibition blocks downstream MAPK signaling, it was hypothesized that addition of a MEKi to a BRAFi would abrogate these effects [Su, 2012]. **Methods:** This 4-part phase I/II study enrolled 365 $BRAF^{V600E/K}$mutated MM pts in Parts B-D. In part C, 162 pts (BRAFi and MEKi treatment-naïve, $\geq$ 18 yrs; ECOG PS $<$2; RECIST measurable disease) were randomized to D monotherapy 150mg BID (D mono) vs. the combination of D (150 mg BID) and T (1 mg or 2 mg QD). Primary endpoints included safety and efficacy. Occurrence of cuSCC (including KA) across three arms in Part C and secondary malignancies with D+T across all Parts are provided below. **Results:** The difference in incidence of cuSCC between D mono and the D+T (150/1) was statistically significant, whereas the difference in incidence between D mono and D+T (150/2) was not. The median time to onset of cuSCC was 30 days in D mono compared to 282 and 152 days with D+T (150/1 and 150/2, respectively). Of 365 pts who received D+T, 2 ($<$1%) cases of new cancers (colorectal and gliobastoma) and 2 ($<$1%) cases of new primary malignant melanoma were reported. **Conclusions:** These data support the experimental hypothesis that the occurrence of cuSCC (including KA) can be substantially reduced and delayed by the addition of a MEKi to BRAFi therapy. Clinical trial information: NCT01072175.

	Treatment groups for Part C		
D	150 mg BID	150 mg BID	150 mg BID
T	--	1 mg QD	2 mg QD
N	53	54	55
Any cuSCC including KA, n (%)	10 (19)	1 (2)	4 (7)
Reduction	--	89%	63%
P value (2-sided)	--	0.0040	0.0901

9017 Poster Discussion Session (Board #5), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

NRAS and *BRAF* mutations in atypical melanocytic lesions arising in melanoma patients treated with vemurafenib.

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Background: BRAF inhibition with targeted therapy has demonstrated improved overall survival in patients with *BRAF* mutant melanoma. The use of the selective BRAF inhibitors vemurafenib and dabrafenib are associated with a range of known and predictable cutaneous side effects, including squamous cell carcinomas often associated with *RAS* mutations. Preclinical evidence indicates that BRAF inhibitors may give rise to non-melanoma tumors by promoting MAPK activation in the tissues that lack mutant BRAF. Here we report atypical melanocytic lesions arising in patients treated with the BRAF inhibitor vemurafenib. **Methods:** To characterize the mutations of both the melanoma tumors and the atypical melanocytic lesions arising in patients with BRAF V600E/K melanoma treated with vemurafenib, a custom Sequenom panel designed to detect 74 mutations in 12 genes known to play a role in the pathogenesis of melanoma was applied to both melanoma and atypical melanocytic lesions for each patient. **Results:** We observed a total of six atypical melanocytic lesions (melanoma in situ and severely dysplastic nevi) in three patients undergoing treatment with vemurafenib. Mutations analysis in both pre-treatment tumor samples and on-treatment melanocytic lesions was feasible in two of the three patients. One patient with *BRAF* V600E metastatic melanoma developed two new melanoma in situ lesions while on vemurafenib, diagnosed 10 and 23 weeks after starting vemurafenib. Both on-treatment melanoma in situ lesions were found by Sequenom analysis to be *BRAF* wild-type, with a *NRAS* Q16R detected in one of the two lesions. Another patient's pre-treatment primary melanoma demonstrated synchronous *BRAF* kinase domain mutations V600K and G466A, and *CTNNB1* D32E mutation; a severely dysplastic nevus which arose after 25 weeks on vemurafenib in this patient showed only a *BRAF*G466A mutation. **Conclusions:** We identified an NRAS mutation and a rare BRAF kinase domain mutation in atypical melanocytic lesions that arose in patients treated with vemurafenib. Further studies are warranted to demonstrate a causal relationship between BRAF inhibition and the development or accelerated growth of atypical melanocytic lesions.

9018 Poster Discussion Session (Board #6), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Identification of changing melanocytic lesions in patients on BRAF inhibitor therapy.

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Background: Patients treated with BRAF inhibitors (BRAFi) have been observed to develop new primary melanomas. In addition, these patients often develop new nevi and involuting nevi. It remains a challenge to detect clinically subtle and histopathologically early melanomas in a background of such increased nevus volatility. In this study, we sought to quantify and describe the new, changing, and involuting melanocytic lesions observed in these patients. **Methods:** A retrospective chart and image analysis was conducted for all BRAFi treated patients referred to the Dermatology service at Memorial Sloan-Kettering Cancer Center. Initial overview and follow-up images were compared in MIRROR Body Mapping image system, DermaGraphiX software (Canfield Imaging Systems, Fairfield, NJ). A total count of new, changing, and involuting melanocytic lesions was determined in four anatomic areas: upper back, lower back, chest, and abdomen. Dermoscopy images of all changing lesions that were biopsied were evaluated for dermoscopic pattern and for the presence or absence of any melanoma specific features. **Results:** Average photography follow-up was 261 days (n=21). The average number of combined new and changing melanocytic lesions was 13.1, 16.4, 9.5, and 6.1 for the upper back, lower back, chest, and abdomen respectively. The average number of involuting melanocytic lesions was 8.0, 4.0, 4.3, and 3.4 for the upper back, lower back, chest, and abdomen respectively. Of all new and changed lesions, 38 were biopsied revealing 31 benign melanocytic lesions and 7 melanomas (18% of lesions biopsied). All 7 melanomas revealed at least one melanoma specific structure, with the most significant dermoscopic discriminate being negative network. **Conclusions:** Given the setting of highly volatile melanocytic changes in BRAFi treated patients and that 18% of biopsied lesions were melanomas; we propose the use of total body photography and dermoscopy as a method for the identification and monitoring of secondary atypical pigmented lesions.

9019 Poster Discussion Session (Board #7), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

NRAS mutation: A potential biomarker of clinical response to immune-based therapies in metastatic melanoma (MM).

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Background: NRAS mutant (mut) MM comprises a distinct, molecularly defined cohort of this disease that appears to have a poor prognosis compared to other genetic subsets. In contrast to BRAF mut MM, there are no effective small molecule inhibitors specifically targeting NRAS. Immune based therapy (IT) has become a mainstay in MM treatment, especially in BRAF wild type (WT) patients (pts). Biomarkers to predict which pts will benefit from IT have not been validated. The goal of this study was to evaluate whether genetic subtype (specifically NRAS) has a role in predicting benefit from IT in BRAF WT MM. **Methods:** We identified 173 pts from 3 institutions who underwent clinical genotyping (exome or PCR based) for NRAS and BRAF mutation from 1/09 – 8/12 and were treated with IT (defined as IL-2, ipilimumab (ipi), or anti-PD-1 (nivolumab, MK3475)/ PD-L1 (MPDL3280A)). Only BRAF WT pts were included. Primary endpoints were response rate (RR) and clinical benefit rate (CBR), defined as RR + stable disease lasting >24 wks to IT (best response as assessed by treating clinicians in any line of IT). Secondary endpoints were overall survival (OS) and progression-free survival (PFS) from first line IT. **Results:** Of the 173 pts, 59 had NRAS mut MM compared to 114 WT/WT (no mutation in NRAS or BRAF). Improved clinical outcomes were seen in the NRAS mut compared to WT/WT cohort in terms of RR (32% vs. 18%, p=0.042), and CBR (49% vs. 30%, p=0.012). Improvements in PFS and OS did not reach statistical significance. By specific IT, NRAS mutation predicted benefit compared to WT/WT for anti-PD-1/PD-L1 (RR 78% vs. 19%, p=0.002; CBR 78% vs. 29%, p=0.013, n=30) and ipi (RR 18% vs. 12%, p=0.315; CBR 41% vs. 22%, p=0.018, n=137). No significant differences were observed with IL-2 (RR 33% vs. 28%, p=0.730; CBR 33% vs. 39%, p=0.741, n=33). **Conclusions:** This study demonstrates that pts with NRAS mut MM achieve increased clinical benefit from IT compared to pts with BRAF/NRAS WT MM. A larger, prospective analysis is necessary to validate and expand on these results, including those with BRAF mut and KIT mut MM. However, our data suggest that NRAS mutation status may be a biomarker of response to IT in MM and that molecularly targeted immunotherapy may be feasible.

9020 Poster Discussion Session (Board #8), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Tumor-specific circulating cell-free DNA (cfDNA) to predict clinical outcome in BRAF V600 mutation-positive melanoma patients (pts) treated with the MEK inhibitor trametinib (T) or chemotherapy (C).

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Background: Tumor-derived cfDNA in the blood is a potential alternative source to derive tumor mutation (mut) status and could be a useful biomarker of therapeutic response. Data from METRIC (NCT01245062), an open-label randomized Phase III study evaluating the efficacy and safety of T vs C, were used to assess: correlation between baseline tumor and cfDNA BRAF muts; correlation between baseline cfDNA levels and tumor burden (i.e., the sum of target lesion diameters); and efficacy based on baseline cfDNA BRAF mut status. **Methods**: BRAF mut status was established for 322 pts using an allele-specific PCR assay in tumor samples. Baseline plasma samples were available for 305/322 pts. cfDNA BRAF mut status was evaluated by Inostics GmBH using BEAMing technology. Spearman correlation coefficients were used to determine the association between cfDNA fraction (mut DNA molecules $> 0.01\%$) and baseline tumor burden. A Cox proportional hazards model was used to assess the association between cfDNA mut status and progression-free survival (PFS). **Results:** The overall agreement between tumor and cfDNA BRAF V600E and V600K mut status was 77%, and 96% respectively. V600E or V600K cfDNA mut fraction did not correlate with baseline tumor burden ($R=0.38$ and 0.23, respectively). Benefit of T vs C was observed regardless of cfDNA BRAF mut status (HR= 0.42, 0.41, 0.47 for V600E, V600K, and not detectable (cfDNA ND) subgroups). Interestingly, cfDNA ND pts had longer PFS vs cfDNA V600E/K pts, independent of treatment ($HR=0.37$ for cfDNA ND vs V600E/K, $p=<0.0001$). For T cfDNA ND median PFS was not reached ($n=52$), however the first quartile was 4.5 months; for V600E ($n=127$) and V600K ($n=21$) median PFS was 3.5 and 4.4 months, respectively. For C median PFS was 3.5, 1.4, and 1.5 months for cfDNA ND ($n=28$), V600E ($n=69$), and V600K ($n=7$), respectively. Similarly, higher response rates were seen in cfDNA ND pts vs cfDNA V600E/K pts across both treatment arms. **Conclusions:** Free circulating DNA can be used to detect BRAF V600 muts. cfDNA mut fraction was not linked to tumor burden. The absence of circulating BRAF mut DNA in BRAF V600 pts may be a marker of a better outcome. Clinical trial information: NCT01245062.

9021 Poster Discussion Session (Board #9), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Genetic variation in immunomodulatory genes as markers of melanoma recurrence-free and overall survival.

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Background: Small reported studies have provided some evidence implicating immune related genes in melanoma susceptibility and prognosis; however candidate selection of these prior efforts has been limited. In this study, we performed an analysis of germline variants in immuno-modulatory genes for their association with melanoma survival in a well characterized cohort of prospectively accrued melanoma patients. **Methods:** Germline DNA isolated from blood samples of 817 melanoma patients was genotyped for 94 SNPs tagging 55 immuno-modulatory genes using Sequenom iPLEX. Cox models were used to test associations between each SNP and recurrence-free and overall survival (RFS and OS), with adjustments for age, gender, subtype, thickness, ulceration, and anatomic site. ROC curves were constructed from different SNP/clinical covariate combinations and the area under the curve (AUC) was used to assess their utility in the classification of 3-year recurrence. **Results:** The SNP rs2796817 in TGFB2 had strong associations with both RFS (HR=3.8, CI 95%: 1.3-11, p=0.02) and OS (HR=5.5, CI 95%: 1.6-19, p=0.029). Other interesting associations with OS came from IRF8 (rs4843861, HR=0.62, CI 95%: 0.39-0.99, p=0.017), CCL5 (rs4796120, HR=7.6, CI 95%: 2.3-25, p=0.035), and CD8A (rs3810831, HR=2.4, CI 95%: 0.91-6.2, p=0.048). A multivariate model including stage, subtype, and one of the SNPs (rs3810831 from CD8A), was shown to improve the AUC when compared to a model including only stage and subtype (0.77 vs. 0.79). **Conclusions:** We identified several immune-related loci associated with melanoma RFS and OS. The strongest association, rs2796817, maps in TGFB2, which among other functions suppresses IL-2 dependent T-cell growth. In addition to other associations found in the study these findings provide evidence for the involvement of immuno-modulatory genes in melanoma prognosis and suggest further investigations of immune related genes in disease progression. This is currently underway in the second stage validation analysis, which includes an expanded set of immune target genes as well as an additional independent cohort of melanoma patients.

9022 Poster Discussion Session (Board #10), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Gene expression profile of primary cutaneous melanomas to distinguish between low and high risk of metastasis.

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Background: Wide variability exists in metastatic rates of primary cutaneous melanoma (CM), even within TNM stage groupings. We developed an RT-PCR based gene expression profile (GEP) test to predict distant metastases in early stage CM. **Methods:** RNA was isolated from formalin-fixed, paraffin embedded biopsies or wide excisions of primary CM from patients with stage 1-4 CM (87% stage 1-2) converted to cDNA and analyzed using RT-PCR. All analyses were done using JMP Genomics and WinSTAT. Radial Basis Machine (RBM) modeling was used to predict metastasis-free survival (MFS) for the training set of 149 samples. Independent validation was performed on an additional 107 CM samples. RBM reports a binary Class 1 (low risk) and Class 2 (high risk). **Results:** Analysis of the training set resulted in a model with 85% receiver operating characteristic (ROC) and sensitivity of 82%. Prediction of metastatic risk for the validation set resulted in a 90% ROC and sensitivity of 89%. 30 of 33 stage 1-3 cases with a known metastatic event were accurately called Class 2. Kaplan-Meier analysis showed 5-year MFS rates of 88% and 25% for predicted Class 1 and Class 2, respectively, in the training set ($p<0.0001$, overall MFS=60%). Similarly, MFS was 95% and 26% for Class 1 and Class 2, respectively, in the independent validation set ($p<0.0001$, overall MFS=67%). Univariate Cox regression analysis of the validation set revealed that GEP, AJCC stage, Breslow thickness, and ulceration were each predictors of metastatic risk (HR=27.2, 11.4, 3.0, and 11.6, respectively, $p<0.002$ for each). Multivariate analysis showed GEP and AJCC stage were independent predictors of risk (HR=8.4 and 6.4 respectively, $p<0.007$ for both). **Conclusions:** This GEP signature provides an accurate stratification of metastatic risk in the training and validation samples independent of all other histologic factors. This test may serve as a prognostic tool for outcomes in patients with melanoma and for stratifying patients for clinical trials.

9023 Poster Discussion Session (Board #11), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Analysis of plasma-based *BRAF* and *NRAS* mutation detection in patients with stage III and IV melanoma.

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Background: Patients with metastatic melanoma are eligible for BRAF inhibitor therapy if the BRAF V600E mutation can be identified in their tumor specimen. Patients lacking an available specimen for genotyping are unable to receive inhibitor therapy. We developed two mutation-specific genotyping platforms and tested their ability to detect BRAF and NRAS mutations in archived plasma and tumor samples to determine the potential utility of blood-based tumor genotyping in melanoma. **Methods:** We analyzed a group of 96 patients with stage III or IV melanoma, prospectively enrolled and followed in the NYU Melanoma Biorepository program. Each patient had a plasma sample and one or more tumor samples available for analysis. We used a combination of allele-specific PCR (Taqman) and SNaPshot assays to identify BRAF V600 and NRAS Q61 mutations in the tumor and plasma samples. **Results:** Among the 96 patients, 51 had stage III disease at the time of analysis; 45 had stage IV disease. Seventy-two patients had 2 or more tumor samples available for analysis, for a total of 204 tumors analyzed. In total, 52/96 (54%) patients had one or more BRAF or NRAS mutant tumors, including one patient with separate BRAF and NRAS mutant tumors (BRAF, n=35 (36%); NRAS, n=18 (19%)). We successfully amplified plasma DNA from 39/52 (75%) patients with tumor-associated mutations. Among those patients with amplifiable plasma DNA we detected mutations in 7 (18%) patients including 3 BRAF V600E, one V600K, 2 NRAS Q61K and one Q61L. Plasma-based mutations matched tumor-associated mutations in all 7 patients. All 7 patients had active disease at the time of blood draw. There were 32 patients with tumor-associated mutations in which a mutation could not be detected in the plasma. Only 15 of those 32 (47%) had active disease at the time of blood draw. There were no mutations detected in the plasma of the 44 patients whose tumors lacked BRAF or NRAS mutations. **Conclusions:** These data suggest that plasma-based detection of BRAF and NRAS mutations has a high specificity for tumor-associated mutations. It may prove to be a useful adjunct to tumor-based genotyping in patients with active disease, especially those lacking an available tumor specimen.

9024 Poster Discussion Session (Board #12), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Pretreatment levels of absolute and relative eosinophil count to improve overall survival (OS) in patients with metastatic melanoma under treatment with ipilimumab, an anti CTLA-4 antibody.

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Background: Ipilimumab, a fully human monoclonal Ab directed against the CTLA-4 receptor on T-cells, has shown significant improvement in OS for patients with metastatic melanoma in randomized phase III trials. Eosinophilia in peripheral blood of those patients has been observed, but its clinical significance as a prognostic factor has not been assessed. **Methods:** We report on a retrospective multi-center analysis of 123 patients who received ipilimumab in three centers between 2010 and 2013. Patients treated had AJCC unresectable stage III or stage IV melanoma of any origin and received ipilimumab in first- and second-line setting at the approved standard dosage of 3mg/kg (4 times q21d). Four patients were excluded due to missing baseline values in eosinophil count (EC). **Results:** Median OS for patients in final analysis (n=119) was 9.57 months. Based on cut-offs assessed by ROC curves, OS was estimated by Kaplan-Meier curves. Baseline absolute eosinophil count (AEC) ≥ 0.1 (10^9/l) was significantly associated with improved OS ($p= 0.002$) with 6-, 12- and 18-month survival rates of 79%, 60% and 48% compared to rates of 48%, 37% and 19% for pts with baseline AEC below 0.1. Baseline relative eosinophil counts (REC) of $\geq 1.75\%$ showed an even stronger significance ($p<0.0001$) with 6-, 12- and 18-months survival rates of 79% vs. 52%, 60% vs. 40% and 51% vs. 17.1% respectively. **Conclusions:** This retrospective analysis elucidates the possible association of baseline EC with OS of patients treated with Ipilimumab. Improvement of OS was highly significant in both analyses considering AEC ($p= 0.002$) and REC ($p<0.0001$). Since easily detectable biomarkers could be of great potential value, further effort on understanding the potential role of eosinophil granulocytes as possible effector cells in the immune-mediated response to anti CTLA-4 abs should be undertaken.

9025 Poster Discussion Session (Board #13), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Analysis of BRAF and NRAS mutation status in advanced melanoma patients treated with anti-CTLA-4 antibodies: Association with overall survival?

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Background: Ipilimumab and tremelimumab are human monoclonal antibodies against cytotoxic T-lymphocyte antigen-4 (CTLA-4). Ipilimumab was the first agent to show a statistically significant benefit in overall survival with durable-long-term responses for advanced melanoma patients both in first-and second-line setting. Up to date, there is no proven association between the BRAF-V600E mutation and the disease control rate (DCR) in response to Ipilimumab. Moreover, significantly shorter survival rates have been reported in patients harboring an NRAS mutation than in those without. This retrospective analysis was carried out to assess if BRAF (V600) and NRAS mutation status affects the clinical outcome of Ipilimumab-treated melanoma patients. **Methods:** This is a retrospective multi-center analysisof 71 patients, with confirmed BRAF and NRAS mutation status, treated with anti-CTLA-4 antibodies from December 2006 until August 2012. The cut-off for the estimation of overall survival was end of November 2012. **Results:** The median overall survival of BRAFV600/NRAS mutant patients (n=44) was 1,41 years compared with 2.67 years in BRAF/NRAS wild-type patients (n=27). Although this difference was not statistically significant there was a trend for improved survival in wild-type patients. Of the 71 patients analyzed, 56 received chemotherapy prior to Ipilimumab. In the BRAF/NRAS mutant cohort, 12 patients received Ipilimumab following either a BRAF- or a MEK- inhibitor. Of those 12 patients, 8 progressed and were unable to complete Ipilimumab. Of the 4 patients who completed 4 cycles of Ipilimumab, 2 were subsequently treated with a BRAF inhibitor. Furthermore out of the 71 patients, 8 patients received a BRAF or a MEK inhibitor after progression; 5 of them are still alive. **Conclusions:** This is the first retrospective study to evaluate the association of both BRAF and NRAS mutational status with the overall survival of Ipilimumab-treated patients. There was a trend towards an improved survival in the BRAF/NRAS wild-type subpopulation. Additional patients will be examined to foster these preliminary results.

9026 Poster Discussion Session (Board #14), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase II study of the multitargeted kinase inhibitor lenvatinib in patients with advanced BRAF wild-type melanoma.

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Background: Lenvatinib is an oral receptor tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFRβ. Melanoma responses in the phase I study led to this multicenter phase II trial of lenvatinib in separate cohorts of BRAF mutant and BRAF wild-type (wt) melanoma to provide an estimate of efficacy and to identify molecular correlates of clinical benefit. Primary analyses of clinical outcomes for the BRAF wt cohort are reported here; the BRAF mutant cohort will be presented at a later date. **Methods:** Eligible patients (pts) had stage IV or unresectable stage III BRAF wt melanoma with $\geq$1 prior treatment (26/96 [27%] pts received $\geq$3 treatments) and no prior VEGF-targeted therapy. Lenvatinib 24 mg once daily with dose reduction for toxicity was administered until disease progression or unmanageable toxicities. Primary endpoint was response rate by independent review (IRR) using RECIST 1.1. Archival tumor tissue and baseline and posttreatment serum samples were collected for molecular analysis. **Results:** 93 pts were treated (median [m] age: 64 y; male: 69%; 95% AJCC stage IV). Confirmed partial responses (PRs) were observed in 8 pts (9%) with a clinical benefit rate (CR+PR+durable SD $\geq$23 wks) of 32% by IRR. mPFS was 3.7 mos (95% CI, 2.5-4.0) by IRR and mOS was 9.5 mos (95% CI, 8.3-12.9); 46% pts required dose reduction for management of toxicity; 12% were withdrawn from therapy due to toxicity. Treatment-related adverse events reported in $\geq$20% pts included hypertension 59% (34% Gr 3/4), fatigue 58% (16% Gr 3/4), nausea 44% (3% Gr 3/4), diarrhea 43% (2% Gr 3/4), decreased appetite 38%, vomiting 29% (2% Gr 3), dysphonia 27%, and proteinuria and headache 26% each (4% and 1% Gr 3/4). Serum biomarker analysis showed baseline levels of serum angiogenic factors, such as angiopoietin-2, correlated with OS. More extensive biomarker analyses are reported in an accompanying abstract. **Conclusions:** Lenvatinib administered to pts with advanced BRAF wt melanoma was associated with frequent but manageable toxicity. Clinical benefit was seen in some pts. Predictive biomarkers for response to lenvatinib, such as the serum level of angiogenic factors, may be useful for future clinical trials. Clinical trial information: NCT01136967.

9027 Poster Discussion Session (Board #15), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Lenvatinib combined with dacarbazine versus dacarbazine alone as first-line treatment in patients with stage IV melanoma.

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Background: Lenvatinib (E7080; LEN) is an oral, receptor tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT and PDGFRβ . In a phase I study qd dosing of >/= 20mg LEN demonstrated PRs and prolonged SD in patients (pts) with advanced melanoma. Dacarbazine (DTIC) upregulates the proangiogenic factor VEGF and has been shown to confer resistance in melanoma cell lines (Lev, JCO 2004; 22:2092-2100). Treatment of melanoma pts with LEN + DTIC may potentiate the therapeutic effects of DTIC. **Methods:** This was a phase II study in pts with metastatic melanoma randomized 1:1 to receive LEN (20 mg QD) + DTIC (1000 mg/m^2 Q 21 d) or DTIC (1000 mg/m^{2}Q 21 d). Pts were stratified by LDH level and stage IV subclass. Eligible pts were ECOG PS 0/1 and had no prior systemic therapies. BRAF status was determined from circulating tumor DNA. The primary endpoint was PFS by independent assessment. **Results:** In a modified ITT analysis,a total of 78 of 81 pts were evaluable for efficacy; 59% were male, 59% were Stage IV M1c, 22% had elevated LDH, 29% had prior adjuvant therapy and 49% BRAF wild-type (*wt*). Most common AEs in the LEN + DTIC arm were hypertension (48%), nausea (38%), constipation (33%), and diarrhea (31%). Most common Grade 3/4 AEs in LEN + DTIC were hypertension (26%) and neutropenia (10%). There were no deaths due to an AE. Median PFS increased in LEN + DTIC compared to DTIC alone (see Table). An improvement in median PFS was observed in BRAF*wt* pts on the combination. **Conclusions:** A 2.7-fold increase in the median PFS was observed in pts administered LEN + DTIC compared to single agent DTIC. A 2.5 fold increase in the median PFS was observed in the combination arm in pts with BRAF*wt* melanoma. The AE profile observed with the LEN + DTIC was consistent with observed LEN monotherapy studies. These data suggest further evaluation of LEN + DTIC in BRAF*wt* melanoma is warranted. Clinical trial information: NCT01133977.

	LEN + DTIC (n=40)		DTIC (n=38)
# Events (%)	30 (75)		30 (79)
Median PFS, wks (95% CI)	19.1 (9.6, 25.6)		7.0 (5.6, 15.6)
HR (95% CI)		0.4 (0.23, 0.75) p value = 0.0033	
BRAF*wt*, median PFS, wks (95% CI) (# events/# pts w/BRAF*wt*)	23.9 (6.1, 42.4) (n=11/17)		9.3 (5.3, 16.9) (n=18/20)
BRAF*mut*, median PFS, wks (95% CI) (# events/# pts w/BRAF*mut*)	6.3 (5.3, 42.0) (n=5/5)		6.0 (5.3, 9.3) (n=3/4)

9028 Poster Discussion Session (Board #16), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Initial results from a phase I, open-label, dose escalation study of the oral BRAF inhibitor LGX818 in patients with BRAF V600 mutant advanced or metastatic melanoma.

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Background: LGX818, a potent and selective BRAF inhibitor (BRAFi) being investigated in BRAF V600 mutant melanoma, has unique biochemical properties with a dissociation half-time $>$ 10 times longer than other BRAF inhibitors. **Methods:** A phase I trial of LGX818 administered orally once (qd) or twice (bid) daily in BRAF V600 tumors was initiated to define the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) and to assess pharmacokinetics and clinical activity in BRAFi–naive or pretreated patients with BRAF V600 mutant advanced melanoma. Baseline assessment of biomarkers from MAPK/PI3K pathways and pharmacodynamics were also evaluated. **Results:** Fifty-four patients have been enrolled in the dose-escalation phase (dose levels [DLs], 50-700 mg qd [n=42] and 75-150 mg bid [n=12]). LGX818 plasma concentrations increased proportionally by dose with a mean $t_{1/2}$ of 4 hours and steady state in $\approx$ 15 days. The MTD/RP2D (450 mg qd) was well tolerated. Seven patients had a dose limiting toxicity (DLT): 5 at qd (1 each with hand-foot skin reaction [HFSR], foot pain, fatigue, diarrhea/rash, insomnia/asthenia) and 2 at bid (1 facial paresis/confusion, 1 musculoskeletal pain/neuralgia). All DLTs were grade 3 and reversible. The most common adverse events ($\geq$ 20%) suspected to be treatment related were cutaneous (rash, dry skin, HFSR, pruritus, keratosis pilaris, alopecia), pain in extremity, arthralgia, and fatigue. Squamous cell carcinoma was observed in 2 patients (1 naive and 1 pretreated). As of 30 Sept 2012, the preliminary efficacy (all DLs) in patients with at least 1 postbaseline tumor assessment was 16 partial responses [PRs] (67%; 12 confirmed) out of 24 BRAFi–naive patients and 2 PRs (8.3%; 1 confirmed) among 24 BRAFi–pretreated patients. Responses were seen at all DLs from 50 to 550 mg qd. Updated safety and efficacy including time to event endpoints will be reported. **Conclusions:** Initial results from this study identified the MTD/RP2D as 450 mg/day and provided an early sign of promising activity in advanced melanoma. Expansion cohorts are ongoing in BRAFi–naive and BRAFi–pretreated melanoma and colorectal cancer. Clinical trial information: NCT01436656.

9029 Poster Discussion Session (Board #17), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Preliminary results from a phase Ib/II, open-label, dose-escalation study of the oral BRAF inhibitor LGX818 in combination with the oral MEK1/2 inhibitor MEK162 in *BRAF* V600-dependent advanced solid tumors.

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Background: Clinical data indicate that combining a BRAF and a MEK inhibitor (BRAFi, MEKi) may be more effective than BRAFi monotherapy in *BRAF*-mutant metastatic melanoma and that a MEKi may overcome or delay resistance to a BRAFi. **Methods:** This ongoing phase 1b/2 study is evaluating the combination of LGX818, a potent, selective BRAF inhibitor, and MEK162, a selective MEK1/2 inhibitor, in BRAFi-naive and -pretreated patients with *BRAF*-mutant tumors. The objective of the phase 1b part is to determine the maximum tolerated dose and/or recommended phase 2 dose (RP2D) for oral, daily LGX818 + MEK162 in *BRAF* V600–mutant advanced solid tumors. A Bayesian logistic regression model with overdose control guides the treatment dose escalation. **Results:** As of January 8, 2013, 20 patients (7 BRAFi-naive melanoma; 9 BRAFi-pretreated melanoma; 2 BRAFi-naive thyroid cancer; 1 BRAFi-naive metastatic colorectal cancer; 1 BRAFi-pretreated colorectal cancer) were treated with LGX818 qd + MEK162 bid at the following dose levels (DLs): 50 mg + 45 mg, 100 mg + 45 mg, 200 mg + 45 mg, and 400 mg + 45 mg. No dose-limiting toxicity has been observed at these DLs. The next DL of 600 mg + 45 mg is under investigation. The single agent RP2Ds for LGX818 and MEK162 are 450 mg and 45 mg, respectively. The most common adverse events (≥ 20%, all grades) suspected to be treatment related were nausea, abdominal pain, and headache. No events of fever, hand-foot-skin reactions, hyperkeratosis, or squamous cell carcinoma were observed. In patients with at least 1 post-baseline CT scan available for investigator-determined response, a complete response was observed in 1/7 (14%) BRAFi-naïve melanoma patients and partial responses were observed in 5/7 (71%) BRAFi-naive melanoma patients, 2/9 (22%) BRAFi-pretreated melanoma patients (starting at 50 mg + 45 mg DL), and 1/2 thyroid cancer patients. **Conclusions:** Preliminary data from this study indicate that LGX818 + MEK162 can be safely combined with promising clinical benefit. No febrile events or photosensitivity were reported suggesting a distinct safety profile for this BRAFi/MEKi combination vs others. Clinical trial information: NCT01543698.

9030 Poster Discussion Session (Board #18), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase III trial of *nab*-paclitaxel versus dacarbazine in chemotherapy-naive patients with metastatic melanoma: A subanalysis based on *BRAF* status.

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Background: Activating mutations of *BRAF* V600 can be found in 40%-50% of melanomas and are related to poor prognosis. In a phase 3 trial for the treatment of metastatic melanoma (MM) in chemotherapy-naive patients, *nab*-paclitaxel (*nab*-P) vs dacarbazine (DTIC) demonstrated a significant improvement in the primary endpoint of progression-free survival (PFS), assessed by independent radiological review (IRR), and a trend toward prolonged overall survival (OS) at the interim survival analysis. The study also explored the effect of *BRAF* status on the efficacy parameters. **Methods:** Chemotherapy-naive patients with stage IV melanoma (M1c stage 65%; elevated LDH 28%) and ECOG performance status 0-1 were randomized to *nab*-P 150 mg/m^2 on days 1, 8, and 15 of a 28-day cycle (n = 264) or DTIC 1000 mg/m^2 on day 1 of each 21-day cycle (n = 265) independent of *BRAF* status. Prespecified subgroup analyses of final PFS and interim OS in subgroups by *BRAF* status (V600E mutant, wild-type, or unknown) were performed. **Results:** *BRAF* mutation status was balanced between the treatment arms, with 36% and 38% of patients with known *BRAF* mutation status in the *nab*-P and DTIC arms, respectively. Patient characteristics were also balanced within *BRAF* subgroups. As shown in the Table, advantage in the *nab*-P arm vs DTIC arm was observed for both PFS and interim OS regardless of *BRAF*mutation status. Poststudy BRAF inhibitor treatment was also balanced. **Conclusions:** In this phase III trial, treatment effect was independent of *BRAF* mutation status, benefiting all patients who received *nab*-P vs DTIC. Therefore *nab*-P should be considered in the armamentarium for all chemotherapy-naive patients with MM. Clinical trial information: NCT00864253.

	nab-P		DTIC			
	N	Median, mo (95% CI)	N	Median, mo (95% CI)	HR	P value
PFS by IRR						
Wild type	116	5.4 (3.5-5.7)	108	2.5 (1.9-3.7)	0.715	0.088
V600E	65	5.3 (3.5-7.5)	67	3.5 (1.9-5.5)	0.883	0.656
Unknown	83	3.7 (2.8-5.6)	90	2.2 (1.9-3.6)	0.684	0.066
Interim OS						
Wild type	116	12.7 (10.0-15.5)	108	11.1 (9.5-14.7)	0.845	0.330
V600E	65	16.9 (11.6- NE)	67	11.2 (8.3-15.3)	0.688	0.132
Unknown	83	11.1 (7.9-13.2)	90	9.9 (6.2-14.1)	0.837	0.381

NE = upper limit was not estimable.

9031 Poster Discussion Session (Board #19), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Sunitinib versus dacarbazine as first-line treatment in patients with metastatic uveal melanoma.

Joseph J Sacco, Paul D. Nathan, Sarah Danson, Paul Lorigan, Steve Nicholson, Christian Ottensmeier, Philippa Corrie, Neil Steven, Andrew Goodman, James M. G. Larkin, T. R. Jeffry Evans, Satish Kumar, Sarah E Coupland, Paul Silcocks, Ernie Marshall; Clatterbridge Cancer Centre, Merseyside, United Kingdom; Mount Vernon Cancer Centre, Northwood, United Kingdom; Cancer Research Centre, Weston Park Hospital, Sheffield, United Kingdom; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Charing Cross Hospital, London, United Kingdom; Southampton University Hospitals NHS Foundation Trust, Southampton, United Kingdom; Oncology Centre, Addenbrooke's Hospital, Cambridge, United Kingdom; Queen Elizabeth Hospital, Birmingham, United Kingdom; Royal Devon and Exeter Hospital, Exeter, United Kingdom; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Velindre Cancer Centre, Cardiff, United Kingdom; Pathology, Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom; University of Liverpool, Liverpool, United Kingdom

Background: Uveal melanoma (UM) is a rare cancer with a propensity for metastasis. There are no effective systemic therapies for metastatic UM, although dacarbazine is commonly used in practice. Sunitinib is a tyrosine kinase inhibitor with activity against several targets including c-Kit and VEGF receptors, both of which have been implicated in the pathogenesis of UM. **Methods:** In this randomized multicentre, phase II study (SUAVE), patients (pts) with metastatic UM, ECOG PS 0-2, and no prior systemic therapy for advanced disease, were randomized 1:1 to sunitinib (50mg daily for 28 days, followed by a 14 day break), or dacarbazine (1000 mg/m^{2}once every 21 days). Crossover was permitted on progression. The primary endpoint was PFS; secondary endpoints included response rate and OS. A sample size of 124 was planned, with a power of 0.9 to detect an increase in 3 month PFS from 0.2 to 0.4 (HR: 0.563) and a one-sided alpha of 0.05. A preplanned futility analysis was performed after 50% of events, and recruitment stopped early, due to low conditional power (0.17% under current trend). Presentation of results was approved by DMC. **Results:** 74 pts from 12 centres were randomized over 24 months. Overall response rates of 0% and 8% were observed in the sunitinib and dacarbazine arms; while stable disease was observed in 24% of pts on sunitinib, and 11% on dacarbazine. PFS and OS were not improved with sunitinib (see Table). 11 pts in the sunitinib arm and 23 in the dacarbazine arm underwent crossover on progression. No unexpected AEs were observed, and no deaths due to toxicity occurred. **Conclusions:** In these preliminary results sunitinib did not have significant clinical activity in metastatic UM. This trial is one of the largest undertaken in metastatic UM and demonstrates that timely recruitment to collaborative multicentre randomized trials is achievable in this rare disease. Clinical trial information: 75033520.

	Sunitinib (n= 38)		Dacarbazine (n= 36)		Hazard ratio (sunitinb:dacarbazine)
	Median in months (95% CI)	Events	Median in months (95% CI)	Events	(95% CI)
PFS	2.76 (2.63 to 4.67)	28	3.88 (2.7 to 8.06)	25	1.09 (0.62 to 1.92)
OS	6.35 (3.29 to 8.42)	24	8.65 (6.25 to 13.55)	21	1.59 (0.86 to 2.96)

Analysis performed on an ITT basis using Cox regression stratified on Helsinki Prognostic Index.

9032 Poster Discussion Session (Board #20), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Final efficacy results of NCIC CTG IND.202: A randomized phase II study of recombinant interleukin-21 (rIL21) in patients with recurrent or metastatic melanoma (MM).

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Background: rIL21 is a T-cell derived cytokine with antitumor activity dependent on NK cells or CD8+ T cells through induction of central and effector memory cells. A previous phase II study demonstrated an ORR of 22.5% in previously untreated patients with MM. We conducted a multicentre randomized phase II study of MM evaluating the efficacy, toxicity, pharmacokinetics, immunogenicity, and biomarkers of rIL21 versus dacarbazine (DTIC). **Methods:** Eligible patients: Recurrent or MM, with either maximum tumour lesion size of < 50 mm or LDH < 2.5 x ULN and prior therapy with BRAF/MEK inhibitors allowed. Patients were treated with either rIL-21, 30 μg /kg/day dose IV daily x 5 days weeks 1, 3, 5 q 8 weeks or dacarbazine (DTIC) 1000 mg/m2 IV q 3 weeks. The primary objective was to compare progression free survival (PFS). The trial was designed to detect a hazard ratio of 1.75 with one-sided alpha of 0.1; 58 progression events were required to provide 80% power. **Results:** 64 patients were randomized, 32 in the rIL-21 arm and 32 in the DTIC arm. The Table summarizes key demographic and efficacy endpoints. Common rIl21 related adverse events were fatigue, rash, diarrhea, nausea, myalgia and elevated liver enzymes. At least one dose reduction/ interruption or discontinuation occurred in 32 (100%) and 27 (96.4%) of rIL21 and DTIC patients. **Conclusions:** Despite encouraging efficacy in prior phase I/II studies, the results suggest that rIL-21 is comparable to DTIC in this patient population. Additional biomarker analysis from this study is pending and combination studies are currently ongoing. Clinical trial information: NCT00514085.

Demographic	rIL-21	DTIC	Total
Patients randomized n	32	32	64
Patients treated n	32	28	60
ECOG PS n (%)			
0	21 (65.6)	22 (68.8)	43 (67.2)
1	11 (34.4)	10 (31.3)	21 (32.8)
Female	9 (28.1)	9 (28.1)	18 (28.1)
Male	23 (71.9)	23 (71.9)	46 (71.9)
Efficacy			
PFS median (months)	1.8(95% CI 1.7, 3.5)	2.0 (95% CI 1.7, 3.5)	
PFS 6 months	19%	30%	
PFS HR (95% CI)			1.1 (0.60, 2.01); p=0.76
OS median (months)	6.6 (95% CI 5.9, 12.3)	7.3 (95% CI 5-0, inf)	
OS 12 months	32%	35%	
OS HR (95% CI)			0.8 (0.38, 1.68); p=0.55
Response rate (CR+PR)	4/30 = 13.3%	4/28 = 14.3%	
95% CI	3.8, 30.7	4.0, 32.7	
Median duration response (months)	5.2	NR	

9033 Poster Discussion Session (Board #21), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Observation after a positive sentinel lymph node biopsy in patients with melanoma.

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Background: The therapeutic benefit of completion lymph node dissection (CLND) in melanoma patients with a positive sentinel lymph node (SLN) remains unknown. This study describes the natural history of selected patients undergoing nodal observation (no-CLND) after a positive SLN biopsy and compares outcomes with those undergoing immediate CLND. **Methods:** A prospective database was used to identify melanoma patients with a positive SLN biopsy from 1994 to 2012. Patient and tumor characteristics, reasons for not undergoing CLND, patterns of initial recurrence, and melanoma-specific survival data were analyzed. **Results:** Of 4319 patients undergoing SLN biopsy, 505 (12%) had a positive SLN. 170 (34%) patients underwent nodal observation and 335 (66%) had an immediate CLND. Patients in the no-CLND group were older (65 vs. 56 years, $p<0.001$) and more likely to have lower extremity lesions (43% vs. 30%, $p=0.004$). There were no differences in tumor thickness, Clark level of invasion, presence of ulceration, or degree of SLN tumor between groups. In 89% of cases, the reason to forgo CLND was due to doctor and/or patient decision. Median follow up was 23.5 and 78.5 months for no-CLND and CLND groups and median time to first recurrence was similar at 9 and 12 months ($p=$NS) respectively. There was no difference in regional recurrence rates between groups (20%). Nodal disease as a site of first recurrence occurred in 16% of patients in the no-CLND group compared with 7% of CLND patients ($p<0.001$). In contrast, systemic disease as first site of recurrence occurred in 8% of no-CLND patients compared with 27% of CLND patients ($p<0.001$). While median relapse-free survival was better after CLND (34.5 vs. 20.9 months, $p=0.02$), melanoma-specific survival was similar (not reached, no-CLND vs. 110 months, CLND, $p=0.14$). **Conclusions:** Immediate CLND after a positive SLN biopsy is associated with fewer initial nodal basin recurrences but similar melanoma-specific survival. These results support ongoing equipoise in the two arms of MSLT-II.

9034 Poster Discussion Session (Board #22), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Preoperative imaging for staging of cutaneous melanoma in the United States: A population-based analysis.

Dana Haddad, David Etzioni, Barbara A. Pockaj, Richard J. Gray, Nabil Wasif; Mayo Clinic, Phoenix, AZ

Background: Routine imaging for staging of early stage cutaneous melanoma is not recommended by National Comprehensive Cancer Network (NCCN) guidelines. Besides the low probability of finding metastatic disease, detrimental aspects include false-positives and additive cost. We sought to investigate the use of imaging for staging of cutaneous melanoma in the United States. **Methods:** Patients with newly diagnosed clinically node negative cutaneous melanoma between 2000-2007 were identified from the Surveillance Epidemiology End Results-Medicare registry. Any imaging performed within 90 days following diagnosis was considered a staging study. Patients with metastatic disease were excluded. **Results:** A total of 25,643 patients were identified, of whom 10,775 (42%) underwent imaging. The mean age was 76.1 years, with the majority being male (61.8%) and Caucasian (98.4%). Breakdown by T classification of the primary was as follows: T1 (63%), T2 (17%), T3 (12%), and T4 (8%). A chest Xray was performed for 9,737 (38.0%), while 3,176 (12.4%) underwent advanced staging imaging studies; PET (7.2%), CT (5.9%), MRI (0.6%), and Ultrasound (0.4%). The use of advanced imaging steadily increased over the period of our study from 9.0% in 2000 to 16.3% in 2007 ($p<0.001$). When stratified by T classification, advanced imaging was used for 8.9% of T1, 14.5% of T2, 18.8% of T3 and 27.0% of T4 tumors ($p<0.001$). Similarly, node positive patients (4.7%) underwent advanced imaging 33.4% of the time compared to 11.3% for node negative patients ($p<0.001$). On multivariate analysis, factors predictive of advanced imaging include higher T classification (OR 3.12 T4 vs. T1, CI 2.77-3.52, $p<0.001$), node positivity (OR 2.70, CI 2.36-3.09, $p<0.001$), more recent year of diagnosis (OR 2.01 2007 vs. 2000, CI 1.71-2.37, $p=0.006$), high school education (OR 1.62, CI 1.43-1.83, $p<0.001$), non-Caucasian race (OR 1.37, CI 1.05-1.77, $p=0.018$), and male gender (OR 1.12, CI 1.03-1.21, $p=0.006$). **Conclusions:** Contrary to current recommendations, performance of advanced imaging for staging of early stage cutaneous melanoma is increasing in the Medicare population. Further research is needed to identify factors driving this increase.

9035 Poster Discussion Session (Board #23), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Sequential treatment with ipilimumab and BRAF inhibitors in patients with metastatic melanoma: Data from the Italian cohort of ipilimumab expanded access programme (EAP).

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Background: Ipilimumab and vemurafenib have recently been approved as single agents for the treatment of unresectable or metastatic melanoma. Currently, limited data exist on the sequential treatment with these agents in patients (pts) with the BRAF mutation; here we evaluate the efficacy outcomes of pts enrolled in the EAP in Italy who sequentially received a BRAF-inhibitor and ipilimumab, or vice versa. **Methods:** Ipilimumab was available upon physician request for pts aged ≥16 years with unresectable stage III/stage IV melanoma who had either failed systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were considered for this analysis if they tested positive for the BRAF mutation and had received a BRAF-inhibitor before or after ipilimumab treatment. **Results:** In total, 855 Italian pts participated in the EAP from June 2010 to January 2012 across 55 centres. Out of 173 BRAF positive pts, 93 (53.7%) were treated sequentially with both treatments: 48 pts received a BRAF inhibitor upon disease progression with ipilimumab and 45 pts received ipilimumab upon disease progression with a BRAF inhibitor. As of December 2012, median overall survival was 14.5 months (11.1-17.9) and 9.7 months (4.6-14.9) for the two groups, respectively ($p=0.01$). Among the 45 BRAF inhibitors pretreated pts, 18 (40%) had rapid disease progression (median overall survival: 5.8 months) and were unable to complete all four induction doses of ipilimumab, while the remaining 27 (60%) pts had slower disease progression (median overall survival: 19.3 months) and were able to complete the therapy with ipilimumab. **Conclusions:** These preliminary results suggest that, in BRAF-mutated pts, to start the sequential treatment with ipilimumab can provide a better survival than the reverse sequence. These findings deserve confirmation in a prospective study.

9036 Poster Discussion Session (Board #24), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Vismodegib, a Hedgehog pathway inhibitor (HPI), in advanced basal cell carcinoma (aBCC): STEVIE study interim analysis in 300 patients.

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Background: Therapy options are limited for locally advanced (la) and metastatic (m) BCC. Aberrant Hedgehog (Hh) signaling is the key driver in BCC pathogenesis. Vismodegib, a first-in-class HPI, is approved in the US for use in adults with aBCC. STEVIE is an ongoing study focusing on safety of vismodegib therapy in patients with aBCC. We present data from the third interim analysis (data cutoff: 19 October 2012), which also permits a preliminary assessment of efficacy of vismodegib in the largest study ever conducted in patients with aBCC. **Methods:** Adult patients with laBCC or mBCC received oral vismodegib 150 mg QD until progressive disease, unacceptable toxicity, or withdrawal. Safety is the primary objective of STEVIE (Common Terminology Criteria for Adverse Events 4.0). Secondary endpoints include efficacy variables. Recruitment is ongoing. **Results:** This analysis included 300 patients with locally advanced (n=278) or metastatic (n=22) BCC from 11 countries with potential for ≥3-month follow-up. Median treatment duration, including vismodegib interruption, was 176.5 days (range 1-455 days). Common treatment-emergent AEs (TEAEs), typically ≤ grade 2, included muscle spasm (59.3%), alopecia (49.3%), and dysgeusia (41.0%) and were comparable to prior analysis. Serious TEAEs occurred in 53 patients (17.7%). 131 (43.7%) discontinued from the study, mainly due to patient or investigator request (n=41), AEs (n=35), disease progression (n=18) or death (n=13; 7 due to AEs assessed by the investigator as unrelated to study drug, 3 due to AEs not possible to be assessed, 3 due to disease progression). Preliminary best overall response in patients with available tumor assessments (n=251) included complete response (17.5%), partial response (39.8%), stable disease (39.0%) and progressive disease (2.8%). Patient recruitment and monitoring is ongoing. **Conclusions:** This third interim analysis of STEVIE confirms the previously observed vismodegib safety profile but can also provide further information about the high rate of tumor control with vismodegib in a large series of patients with aBCC. Clinical trial information: 2011-000195-34.

9037 Poster Discussion Session (Board #25), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma (aBCC): 18-month update of the pivotal ERIVANCE BCC study.

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Background: Therapies for aBCC, which includes metastatic (m) and locally advanced (la) BCC, are limited. Abnormal Hedgehog pathway signaling is a key driver in BCC pathogenesis. Primary analysis of the pivotal ERIVANCE BCC trial of vismodegib, an oral hedgehog pathway inhibitor (HPI), demonstrated an objective response rate (ORR) of 30% and 43%, in mBCC and laBCC patients, respectively, with a median duration of response (DOR) of 7.6 months. We present safety and investigator (INV) assessed efficacy results 18 months (29 May 2012) after primary analysis (26 Nov 2010). **Methods:** Multicenter, international, nonrandomized study in patients (N=104) with radiographically measurable mBCC or laBCC (surgery inappropriate due to multiple recurrence, or substantial morbidity or deformity anticipated) receiving 150 mg oral vismodegib daily until disease progression or intolerable toxicity. Key secondary endpoints included INV-assessed ORR, progression-free survival (PFS), DOR, overall survival (OS), and safety. **Results:** At data cutoff, 21 patients continued to undergo protocol-specified assessments and 56 patients were in survival follow-up. The median dose intensity was comparable with primary analysis. ORR was 48.5%, mBCC; 60.3%, laBCC, comparable with primary analysis. However, median DOR improved (mBCC=14.7; laBCC=20.3 months). The median OS for mBCC was 30.9 months but not estimable in laBCC. Adverse events remained consistent, with muscle spasm, alopecia, dysgeusia, weight decrease, and fatigue most frequently reported. Eleven more deaths were reported in the update period after primary analysis; these occurred in survival follow-up and were not drug-related. **Conclusions:** Vismodegib is the first FDA-approved HPI; thus, long-term efficacy and safety data are particularly relevant. 18-month update data confirmed prolonged responses and consistent safety in vismodegib-treated aBCC patients. Clinical trial information: NCT00833417.

9038 General Poster Session (Board #44A), Sat, 8:00 AM-11:45 AM

Phase II study of low-dose peginterferon alfa-2b antiangiogenic therapy in patients with metastatic melanoma overexpressing basic fibroblast growth factor: An Eastern Cooperative Oncology Group study (E2602).

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Background: FGF-2 plays an important role in the pathogenesis and progression of melanoma. In particular, FGF-2 and its receptor are expressed in melanoma cells. We investigated the use of graded dosages Peg-IFN in patients with stage IV melanoma overexpressing FGF-2. Primary objective: suppression of plasma FGF-2 to normal levels ($<$ 7.5 pg/mL). Secondary objectives: clinical efficacy of Peg-IFN and its association with angiogenic factor levels (FGF-2 and vascular endothelial growth factor /VEGF). **Methods:** Patients were eligible if they had stage IV melanoma from any primary site. Prior systemic therapies ($<$ 4) were allowed including IFN. Plasma FGF-2 was measured at baseline (Step 1) and patients with levels $>$ 15 pg/mL allowed to receive study treatment (Step 2). Peg-IFN was given weekly at starting dose of 0.5 mcg/kg/wk with increments every 3 weeks (maximum dose: 5 mcg/kg/wk) based on serial FGF-2 levels. **Results:** 207 patients entered into Step 1 and 45 (22%) overexpressed FGF-2 with a median level of 22 pg/dL (range, 15-216). 29 eligible patients enrolled into Step 2 and received treatment. The median age was 64 years and most had $>$ 2 prior therapies. FGF-2 decreased in 28 (97%) patients with suppression to normal level in 10 (35%). The median time to FGF-2 suppression was 30 days (range, 14-116). The best clinical responses were PR (7%) and stable disease (17%). The median PFS and OS were 2.0 and 9.7 months, respectively. Patients who achieved FGF-2 suppression were more likely to have a response or stable disease compared to those who did not (50% vs 11%; P=.03). Landmark analysis at 63 days showed similar OS between those who achieved FGF-2 suppression and those who did not (7.8 vs 7.7 months; P=.31). VEGF decreased in 27 patients (93%) during treatment and the levels paralleled those of FGF-2 over time. We did not find a compensatory rise in VEGF level among those with FGF-2 suppression. **Conclusions:** Graded dose Peg-IFN suppresses FGF-2 and has activity against metastatic refractory melanoma. Complete suppression of plasma FGF-2 was observed in 35% of the patients and correlated with clinical response but not OS. Clinical trial information: NCT00049530.

9039 **General Poster Session (Board #44B), Sat, 8:00 AM-11:45 AM**

Toward an miRNA signature for predicting outcome in patients with melanoma.

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Background: Melanoma remains a clinical challenge, as an aggressive and often unpredictable tumor. The incidence continues to increase, but treatment options are limited. One significant challenge is predicting which patients with stage I or II disease will have a poor outcome. We sought to develop a tool to assist in risk stratifying patients with melanoma. **Methods:** This is a prospective trial in which patients with melanoma at least 0.5mm deep were enrolled between 2007-2011. Tissue was collected from primary tumors, bulky nodes and metastatic deposits. RNA was extracted, labeled and hybridized to a miRNA microarray (Affymetrix). Hierarchical cluster method was used to find similarities among samples. A clinical patient database was maintained. **Results:** This study looks at 58 intermediate and high risk subjects. The median depth of melanoma was 3mm. The median age was 69 (range 26-95) and most patients (48/58, 83%) were treated with surgery alone, with ten receiving adjuvant therapy. All patients underwent wide excision, and 43 patients had sentinel node biopsy. Twenty-seven patients developed a recurrence (47%), and 19 (33%) patients have died, 14 from melanoma. The median length of follow-up is 21 months (range 1-76 months). A total of 112 probes are differentially expressed at a p value of 0.005. The largest number of differentially expressed probes relate to location of the tumor. Other significant differences are origin of the specimen (primary versus node), mitotic rate and subject age. High expression of miR-193b was correlated with death from melanoma, $p=0.05$. Parameters with no differential expression include gender, tumor depth and subtype, and ulceration. **Conclusions:** Microarray analysis of miRNAs is a reliable platform to obtain prognostic information about melanoma. The miRNA signatures found in this patient population reinforce some well described differences among patients with melanoma, and fail to find a difference between other groups thought to be clinically important. Tumor genetic profiling may provide better risk stratification of patients with melanoma than clinical parameters alone.

9040 General Poster Session (Board #44C), Sat, 8:00 AM-11:45 AM

Adjusting for treatment crossover in the METRIC metastatic melanoma (MM) trial for trametinib: Preliminary analysis.

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Background: In METRIC, a randomized phase III study, trametinib significantly improved PFS (hazard ratio [HR]=0.44 [95% CI 0.31–0.64; p<0.001]) vs chemotherapy (chemo) in patients (pts) with *BRAF V600E+* MM and no brain metastases. Median overall survival (OS), a secondary endpoint, has not yet been reached. OS results are likely to underestimate the effect of trametinib as pts progressing on chemo could cross over to experimental treatment (trt). This analysis attempts to adjust for confounding effects of trt crossover on OS in the overall population and first line (1L) subgroup using current METRIC results. **Methods:** Randomization-based crossover adjustment methods – Rank Preserving Structural Failure Time Models (RPSFTM) and the Iterative Parameter Estimation (IPE) algorithm – were used. We conducted two sets of analyses testing different assumptions regarding the durability of the trt effect. "Trt group" analyses adjusted for crossover under the assumption that the trt effect is maintained until death regardless of trt duration; "On trt – observed" analyses adjusted for crossover under the assumption that the trt effect disappears upon trt discontinuation. Results are presented as HRs. **Results:** 178 and 95 MM pts were randomized to trametinib and chemo, respectively; 49.5% of chemo pts crossed over to trametinib as of data cut off (Oct. 2011). Median follow-up was 4.9 months and 19.8% deaths occurred across both arms. Crossover adjustment results are presented in the Table. **Conclusions:** RPSFTM and IPE "trt group" analyses resulted in OS HR point estimates that represented greater trt effects in the overall population and 1L subgroup compared to the unadjusted HRs. Results are exploratory because few deaths have been observed in the current dataset. Future analyses on a mature dataset should produce more robust estimates of the OS trt effect after crossover adjustment.

		HR (95% CI)	
Assumption	**Adjustment method**	**Overall pts**	**IL pts**
	Baseline unadjusted	0.53 (0.30, 0.94)	0.55 (0.26, 1.13)
Trt group	RPSFTM	0.45 (0.23, 0.87)	0.46 (0.20, 1.07)
	IPE	0.45 (0.23, 0.90)	0.47 (0.21, 1.05)
On trt – observed	RPSFTM	0.48 (0.26, 0.88)	0.56 (0.30, 1.05)
	IPE	0.49 (0.26, 0.91)	0.57 (0.31, 1.03)

9041 General Poster Session (Board #44D), Sat, 8:00 AM-11:45 AM

Ipilimumab retreatment following induction therapy: The expanded access program (EAP) experience.

Kim Allyson Margolin, Omid Hamid, Jeffrey S. Weber, Anna C. Pavlick, F. Stephen Hodi, Asim Amin, Kelly Bennett, Tracy Michener, David R. Minor; University of Washington, Seattle, WA; The Angeles Clinic and Research Institute, Los Angeles, CA; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; Department of Medicine, NYU Langone Medical Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Levine Cancer Institute, Charlotte, NC; Bristol-Myers Squibb, Plainsboro, NJ; California Pacific Center for Melanoma Research and Treatment, San Francisco, CA

Background: Phase III study MDX010-020 for patients (pts) with advanced melanoma showed that retreatment (ReRx) with ipilimumab (Ipi) upon disease progression could result in further clinical benefit (Hodi et al. *NJEM* 2010). The Ipi EAP (CA184-045), conducted from 3/2010 to 3/2011, allowed ReRx with Ipi for a subset of pts with progression after benefit from their initial Ipi (SD for ≥3 months or objective response). **Methods:** Pts with unresectable stage III/IV melanoma who progressed on ≥1 systemic therapies or had no alternative treatment options were eligible for the EAP. Pts who received 3 mg/kg Ipi i.v. q 3 wks up to 4 doses on the EAP were eligible for ReRx using the same regimen if they had not experienced unacceptable toxicity requiring Ipi discontinuation (e.g., grade 4 any severe adverse events (AEs), grade 3/4 immune-related AEs (excluding endocrinopathies)), and had disease progression after clinical benefit defined as ≥3 months SD or objective response, or delayed response following progressive disease not requiring a different interval therapy. Endpoints of this retrospective analysis were clinical benefit defined by objective response or SD ≥3 months and toxicities measured by occurrence of serious adverse events (SAEs), irAEs, or death on study. **Results:** 108/2155 pts (5%) met the eligibility criteria for ReRx. Among these 108 pts, grade 3 drug-related SAEs during initial therapy were endocrinopathies only (4%). During ReRx, grade 3 drug-related SAEs, all <2%, were colitis, diarrhea, GI hemorrhage, fatigue and dehydration, similar to the toxicities of Ipi in the full EAP cohort of 2155 pts. Three pts (3%) of the 108 in this ReRx cohort had drug-related GI SAEs leading to discontinuation of Ipi. Among these pts who underwent ReRx, the median OS from the 1st initial therapy dose was 21.1 months. **Conclusions:** In this analysis of EAP pts who experienced benefit from initial Ipi therapy (including those with durable SD who subsequently progressed) and received ReRx with Ipi, no new safety signals were identified. The potential benefit of Ipi ReRx on OS will be prospectively evaluated in an ongoing phase II study in which pts who qualify are randomized to Ipi ReRx or physician's choice alternative therapy. Clinical trial information: NCT00495066.

9042 General Poster Session (Board #44E), Sat, 8:00 AM-11:45 AM

Investigation of the diagnostic precision and utility of sentinel lymph node biopsy in the treatment of patients with Merkel cell carcinoma (MCC).

Elena Mantas Paulus, Fawwaz Ridwan Shaw, Martin D. Fleming; University of Tennessee Health Science Center, Memphis, TN

Background: Merkel cell carcinoma (MCC) is a relatively uncommon and aggressive cutaneous neuroendocrine neoplasm with a high incidence of local recurrence and regional and distant metastasis. The management and identification of prognostic factors remains of value in the treatment of these patients. Although the optimal multidisciplinary treatment of MCC has yet to be determined, the purpose of this study was to investigate whether sentinel lymph node biopsy confers a lower risk of recurrent disease in patients with Merkel cell carcinoma at our institution. **Methods:** After obtaining institutional review board approvals, all patients with a diagnosis of MCC from 2002-2012 were obtained from our tumor registries. Clinical features, pathologic characteristics, management modalities, and patient outcomes were retrospectively reviewed. **Results:** Of 20 patients with MCC, nine patients underwent sentinel lymph node biopsy, another four received therapeutic lymph node dissections, and seven patients did not have lymph node evaluation at the initial operation. The most common nodal basins involved were cervical and axillary. Recurrent disease was observed in seven patients (35%). Three patients underwent complete regional lymph node dissection after developing clinically positive nodal disease subsequent to only wide local excision at the index operation (15%). Three patients developed locoregional recurrence and the seventh patient developed metastatic disease to the liver. Of these seven patients with recurrent disease, only two (28.57%) had initial lymph node evaluation. Twelve patients (60%) received adjuvant therapy with chemotherapy (carboplatin/etoposide) and/ or radiation therapy. **Conclusions:** Merkel cell carcinoma continues to demonstrate its propensity for high rates of recurrence and metastatic disease. Of the seven patients with recurrent locoregional and/or nodal disease in our study, only two patients had initial lymph node evaluation, which was statistically significant with a p value of 0.01175. Further analysis focusing on additional prognostic factors is necessary to optimize our management algorithms and patient outcomes.

9043 General Poster Session (Board #44F), Sat, 8:00 AM-11:45 AM

Differential genomic profiles of tumor-involved and tumor-free sentinel lymph nodes in patients with melanoma.

Ahmad A. Tarhini, William A LaFramboise, Uma N. M. Rao, Howard Edington, James F. Pingpank, Matthew Peter Holtzman, Hussein Abdul-Hassan Tawbi, Albert Geskin, Amy Rose, Christy Milburn, Michelle Merriman, Cindy Sander, Christin Sciulli, Yan Lin, John M. Kirkwood; University of Pittsburgh Medical Center, Pittsburgh, PA; University Pittsburgh Medical Center, Pittsburgh, PA

Background: For clinical stage I and II node negative melanoma the histologic status of the sentinel lymph node (SLN) is the most significant predictor of survival. Molecular characterization of node positive and node negative SLNs through gene expression profiling may improve the understanding of the molecular mechanisms of metastasis and identify specific gene signatures for SLN+/SLN- that correlate with clinical outcome. **Methods:** We characterized 15 SLN+ and 15 SLN- melanoma patients (T3a/b, T4a/b) who underwent SLN dissection for routine staging using transcriptome profiling analysis on 5μ sections of fresh LN samples. The primary endpoint was mRNA expression profiling using the U133A 2.0 Affymetrix gene chips. Significance Analysis of Microarrays v.4 was used to perform non-parametric analysis and statistical comparison for each transcript corrected for false discovery rate (q value) to control for type 1 errors arising from multiple tests. Pathway analysis was performed using Ingenuity Pathway Analysis software. **Results:** Tumor size ranged from 1-2mm in size. Twenty-one genes were expressed at significantly (q value <0.056) higher levels in SLN+ vs SLN-. These included CCNA2, CEP55, DCT, FEN1, HMMR, MLANA, PAICS, PBK, POSTN, RAB27A, RRM2, SHCBP1, SILV, TYR, CENPE, CCL20, CHEK1, LINS, TPX2, TTK, TYRP1. Pathway analysis (39 genes >1.4 fold; $q < 0.12$) identified the top disease categories as "Cancer" (26 genes, $p = 5.7x10\text{-}9$) and "Dermatological" (14 genes, $p = 3.9x10\text{-}6$). The top functional categories included "Cell Cycle" (21 genes $p= 2.3x10\text{-}12$) and "Cell Growth and Proliferation" (26 genes $p=9x10\text{-}9$). The relevant canonical pathways were "Eumelanin Biosynthesis" ($p=3x10\text{-}5$) and "Cell Cycle: G2/M DNA Damage Checkpoint Regulation" ($p=1.2x10\text{-}4$). **Conclusions:** We identified a 21 gene signature that is consistent with metastatic melanoma and its microenvironment and is differentially expressed in SLNs that are tumor involved. These gene families provide a signature of nodal involvement that may assist in diagnosis, and may be further explored towards prediction of outcome and development of therapy. A validation study is ongoing with clinical outcome association analyses as follow up is mature.

9044 General Poster Session (Board #44G), Sat, 8:00 AM-11:45 AM

Adjusting for treatment crossover in the BREAK-3 metastatic melanoma trial for dabrafenib: Preliminary analysis.

Nicholas Latimer, Keith R. Abrams, Mayur Amonkar, Ceilidh Stapelkamp, R. Suzanne Swann; School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom; Department of Health Sciences, University of Leicester, Leicester, United Kingdom; GlaxoSmithKline, Collegeville, PA; GlaxoSmithKline, Uxbridge, United Kingdom

Background: In BREAK-3, dabrafenib improved PFS (hazard ratio [HR]=0.30 [95% CI 0.18–0.51; p<0.0001] as of Dec 19, 2011) vs dacarbazine (DTIC) in patients (pts) with previously untreated *BRAF V600E*+unresectable or metastatic melanoma. In an updated analysis (data as of June 25, 2012), PFS HR=0.37 (95% CI 0.24–0.58; p<0.0001). Overall survival (OS) results may underestimate the effect of dabrafenib as DTIC pts could cross over to dabrafenib at progression. This analysis attempts to adjust for confounding effects of crossover on OS using BREAK-3 results from June 2012 data. **Methods:** Randomization-based crossover adjustment methods – Rank Preserving Structural Failure Time Models (RPSFTM) and the Iterative Parameter Estimation (IPE) algorithm – were used. We conducted 2 sets of analyses testing different assumptions regarding the durability of the treatment (trt) effect. "Trt group" analyses adjusted for crossover under the assumption that the trt effect is maintained until death regardless of trt duration; "On trt – observed" analyses adjusted for crossover under the assumption that the trt effect disappears upon trt discontinuation. Results are presented as HRs. **Results:** 187 and 63 pts were randomized to dabrafenib and DTIC, respectively. At the time of this analysis, 55.6% of DTIC pts crossed over to dabrafenib. Median duration of follow-up was 10.5 months and 76 (30.4%) pts died. Median OS has not yet been reached. Crossover adjustment results are presented in the Table. **Conclusions:** All RPSFTM and IPE analyses resulted in point estimates for the OS HR that represented a substantial increase in trt effect compared with the unadjusted HR of 0.75. Results are exploratory, as the OS data are not mature. Analyses will be updated when further data are available.

Assumption	Adjustment method	HR (95% CI)
	Baseline unadjusted	0.75 (0.44, 1.29)
Trt group	RPSFTM	0.52 (0.17, 1.61)
	IPE	0.52 (0.18, 1.55)
On trt – observed	RPSFTM	0.57 (0.22, 1.50)
	IPE	0.60 (0.26, 1.41)

9045 General Poster Session (Board #44H), Sat, 8:00 AM-11:45 AM

Current management of advanced melanoma: A European perspective.

Clare Frances Jones, Zhongyun Zhao, Beth L. Barber, Marloes Bagijn, Deborah Saltman; PRMA Consulting Ltd, Fleet, United Kingdom; Amgen, Inc., Thousand Oaks, CA; Imperial College London, London, United Kingdom

Background: Melanoma is a rare but serious subtype of skin cancer that can infiltrate deep skin layers and commonly metastasizes. Although it makes up only a small proportion (<5%) of all skin cancer cases, it causes 75% of deaths from skin cancer. Melanoma affects all ages with 38% of patients less than 55 years old causing significant work productivity and life impact. Median survival of patients with advanced (unresectable or metastatic) melanoma is less than a year. Conventional chemotherapy provides no overall survival benefit. Within the last 2 years, the EMA approved two new drugs for advanced melanoma: ipilimumab for second-line and vemurafenib for patients with *BRAF* mutation-positive tumors; both drugs provide survival benefits. The objective of this study was to investigate physicians' perceptions of the unmet need in the treatment of advanced melanoma in the new treatment landscape. **Methods:** 150 oncologists and dermatologists from France, Germany, Italy, Spain, and the UK who had treated at least 12 patients with advanced melanoma in the last 12 months prior to September 2012 were asked by a web-based survey to describe their treatment of advanced melanoma and the current issues in treatment. **Results:** Overall, 76% of respondents had used ipilimumab and 79% had used vemurafenib in the 12 months prior to September 2012. Toxicity and tolerability of treatment was the most commonly mentioned issue (cited by 43% of respondents). Limited treatment effectiveness (29% respondents) was also highlighted by respondents in all countries. Limited treatment options were identified as a key issue by 30% of respondents in Germany, France, and the UK. Other commonly mentioned issues were low response rates and poor survival. **Conclusions:** The majority of physicians surveyed had experience using vemurafenib and ipilimumab. However, a number of issues remain in the treatment of advanced melanoma, suggesting that unmet need remains high.

9046 General Poster Session (Board #45A), Sat, 8:00 AM-11:45 AM

Open-label, multicenter safety study of vemurafenib in patients with *BRAF^{V600}* mutation–positive metastatic melanoma.

James M. G. Larkin, Michele Del Vecchio, Paolo Antonio Ascierto, Jacob Schachter, Claus Garbe, Bart Neyns, Mario Mandala, Paul Lorigan, Wilson H Miller, Alexander David Guminski, Carola Berking, Piotr Rutkowski, Paola Queirolo, Axel Hauschild, Ana Maria Arance, Michael Paul Brown, Lada Mitchell, Maria Luisa Veronese, Christian U. Blank; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Istituto Nazionale Tumori Fondazione, Naples, Italy; Ella Institute for Melanoma, Division of Oncology, Sheba Medical Center, Tel-Hashomer, Israel; Universität Tübingen – Hautklinik, Tübingen, Germany; UZ Brussel, Brussels, Belgium; Papa Giovanni XXIII, Division of Medical Oncology, Unit of Clinical and Translational Research, Department of Oncology and Hematology, Bergamo, Italy; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Lady Davis Institute and Segal Cancer Center, Jewish General Hospital, McGill University, Montreal, QC, Canada; Melanoma Institute of Australia, Sydney, Australia; Department of Dermatology, Ludwig Maximilian University, Munich, Germany; Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; Department of Medical Oncology A, National Institute for Cancer Research, Genoa, Italy; Universitäts-Hautklinik Kiel, Kiel, Germany; Hospital Clínic, Barcelona, Spain; Royal Adelaide Hospital, Adelaide, Australia; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Hoffmann-La Roche Ltd, Basel, Switzerland; The Netherlands Cancer Institute-Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: Vemurafenib (VEM), a BRAF kinase inhibitor, has demonstrated high response rates and improved progression-free and overall survival in pts with *BRAF^{V600}*mutation–positive metastatic melanoma (mM). We present interim results from predefined subgroups from a large multicenter, open-label safety study of VEM in pts with mM (NCT01307397). **Methods:** Pts with *BRAF^{V600}*mutation–positive histologically confirmed mM received VEM (960 mg BID) as first-line therapy or subsequent to previous therapies. Assessments for safety and efficacy were made every 28 days. **Results:** As of Feb 29, 2012, 2,265 pts have received VEM. Pts had a median age of 54.0 (13-95) yrs and median time since diagnosis of mM of 6.2 (0-351.9) mos. 59% had received prior systemic therapy. Median time of exposure to VEM as of the cut-off date was 3 (0.03-11.24) mos for the overall population and majority of subgroups, and approximately 2.5 mos for pts with ECOG ≥2 and age ≥75 yrs. 1537 (68%) pts were still receiving VEM at the cut-off date. 728 (32%) pts discontinued, most frequently because of PD (538/728 pts; 74%). Adverse events (AEs) were reported for 87% of all patients, with arthralgia (32%) and rash (26%) the most frequent. The incidences of AEs in the subgroups are summarized (Table). Although efficacy analyses are limited by the short duration of follow-up, six-month OS rate was 76% (95% CI 72-79%) and median PFS was 4.1 mos (95% CI 3.9-4.5 mos). Postbaseline tumor assessments were available for 63% and 30% of pts at wk 8 and 16, respectively. At wk 8 CR: 2%, PR: 57%, SD: 30%, PD: 6%. At wk 16 CR: 3%, PR: 46%, SD: 31%, PD: 15%. **Conclusions:** Although the overall safety profile of VEM in this study was consistent with previous clinical data, interim analyses of subgroups suggest that very elderly pts may be at higher risk of G3 AEs. Clinical trial information: NCT01307397.

		AEs, % (95% CI)		
Subgroups	**N**	**G3**	**G4**	**Leading to withdrawal**
Overall	2,265	31 (29-33)	2 (1-3)	4 (3-5)
BM No	1,673	30 (28-32)	1 (1-2)	4 (3-5)
Yes	555	35 (31-39)	3 (2-5)	4 (3-6)
LDH Normal	1,037	31 (28-33)	2 (1-3)	3 (2-4)
Elevated	1,159	32 (29-35)	2 (2-4)	5 (3-6)
ECOG 0-1	1,992	31 (29-33)	2 (1-2)	3 (3-4)
≥2	236	37 (31-43)	4 (2-7)	7 (4-11)
Prior ipilimumab	236	40 (34-46)	4 (2-7)	3 (1-5)
Age (yrs) <75	2,089	30 (28-32)	2 (1-3)	3 (3-4)
≥75	176	44 (36-51)	2 (1-6)	13 (8-18)

9047 General Poster Session (Board #45B), Sat, 8:00 AM-11:45 AM

Biomarker study in patients with resectable AJCC stage IIIc or stage IV (M1a) melanoma treated in a randomized phase II neoadjuvant trial.

Nitin Chakravarti, Doina Ivan, Merrick I. Ross, Joseph L. Ilagan, Carla L. Warneke, Kevin Kim, Nicholas E. Papadopoulos, Suzanne Cain, Jeffrey E. Gershenwald, Marcella M. Johnson, Agop Y. Bedikian, Richard E. Royal, Janice N. Cormier, Ehab Y. Hanna, Jeffrey Edwin Lee, Victor G. Prieto, Wen-Jen Hwu; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Fewer than 30% of patients with resectable stage IIIC or IV (M1a) metastatic melanoma (MetM) who undergo surgical resection will achieve long-term survival. This study was designed to administer neoadjuvant systemic therapy prior to definitive surgery to explore potential predictive and prognostic biomarkers in patients with MetM. **Methods:** Fifty patients with resectable MetM were randomized to receive temozolomide (TMZ) alone at 150 mg/m^2/day x 7 days every other week (Arm A, n=26) or with pegylated interferon (PGI) at 0.5 mcg/kg weekly (Arm B, n=24). After a pre-treatment tumor biopsy, patients received 8 weeks of neoadjuvant therapy before undergoing surgery. Endpoints were clinical response, tolerability, and biomarker analysis by immunohistochemistry and gene array. In particular, we examined PD-1, PD-L1, pAKT, pMAPK, Ki67, and caspase 3. Patients with response (complete-, partial-, or stable disease) received up to 3 additional cycles of the assigned regimen as adjuvant therapy. **Results:** Overall response to neoadjuvant therapy was 38% [1 CR, 15 PRs, 3 SDs]: 31% in Arm A (95% CI 14% - 52%) and 46% in Arm B (95% CI 26% - 67%). Estimated 4-year overall survival was 52.52% (95% CI 35.86 - 66.74%). Only 5 patients did not undergo definitive surgery after neoadjuvant treatment due to development of distant metastasis. Preliminary data indicate that in Arm B, responders had higher PD-1 membranous expression in tumor infiltrating lymphocytes (TILs) (p=0.029). Furthermore, low PD-L1 cytoplasmic expression in TILs (p=0.002) as well as low nuclear PD-L1 expression in tumor cells (p=0.025) had better overall survival. **Conclusions:** Comparing with historical data, neoadjuvant therapy has a potential to improve overall survival in patients with resectable MetM. Biomarker analysis may predict response to neoadjuvant treatment as well as overall survival. Clinical trial information: NCT00525031.

9048 General Poster Session (Board #45C), Sat, 8:00 AM-11:45 AM

Impact of BRAF mutation and effectiveness of BRAF inhibitor on the brain metastases in patients with metastatic melanoma.

Tulasi Gummadi, Roxana Stefania Dronca, Chul Kim, Lisa A. Kottschade, Rajendar K Mittapalli, William F. Elmquist, Arkadiusz Dudek; University of Minnesota, Minneapolis, MN; Mayo Clinic, Department of Medical Oncology, Rochester, MN; Mayo Clinic, Rochester, MN; University of Illinois at Chicago, Chicago, IL

Background: Brain metastases continue to be the major cause of morbidity and mortality in patients with metastatic melanoma. The impact of BRAF mutations and effectiveness of BRAF inhibitors on the brain metastases in these patients is lacking. **Methods:** Preclinical studies were conducted to assessthe steady-state brain and plasma distribution of vemurafenib, a BRAF inhibitor in FVB wild-type and Mdr1a/b-/-Bcrp1-/- mice deficient in the drug efflux transporters, p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP). A retrospective analysis of patients with metastatic melanoma treated at University of Minnesota from August 2011 to December 2012 was conducted. A similar analysis of cases treated at Mayo Clinic is underway. **Results:** The preclinical studies in mice show that both P-gp and BCRP play a significant role in limiting the brain distribution of vemurafenib. Retrospective analysis was performed on 57 patients with Stage IIIc /IV cutaneous and mucosal melanoma. Patients with BRAF mutation had a higher incidence rate of brain metastases compared to patients without BRAF mutation, although it was not statistically significant (Incidence ratio=1.56; 95% CI=0.70-3.48; P=0.27). Vemurafenib neither reduced the incidence of brain metastases (Incidence ratio = 0.89; 95% CI: 0.30-2.60; P=0.83) nor made significant difference in overall survival. It was observed that treatment with BRAF inhibitor led to improvement in extracranial disease but did not affect progression of intracranial disease. **Conclusions:** In concordance with preclinical data which indicates that P-gp and BCRP play a significant role in limiting the brain distribution of vemurafenib, the retrospective analysis shows that there is improvement in extracranial disease but progression in intracranial disease with treatment with BRAF inhibitor in patients with metastatic malignant melanoma with BRAF mutation. Development of BRAF inhibitors that are not substrates for P-gp and BCRP or concomitant use of P-gp and BCRP inhibitors with vemurafenib, may be needed in order to control or prevent intracranial disease in these patients. Further analysis to improve statistical power of our observation is underway.

9049 **General Poster Session (Board #45D), Sat, 8:00 AM-11:45 AM**

Prognostic implication of KIT mutations in melanoma.

Katherine G. Roth, Emily C. Zabor, Marta N. Colgan, Jedd D. Wolchok, Paul B. Chapman, Gary K. Schwartz, Katherine S. Panageas, Richard D. Carvajal; The University of Texas Health Science Center at Houston, Houston, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: The natural history of BRAF and NRAS mutant (mut) melanoma (mel) has been described, but prognostic implications of KIT mut mel have not. **Methods:** We performed a single-center retrospective review of 180 patients (pts) enriched for mucosal, acral or chronic sun-damaged skin (CSD) mel and screened for KIT, BRAF, and NRAS mut from 4/07 - 4/10 as a part of a phase II imatinib study. Pt/disease characteristics were compared using the Kruskal-Wallis or Chi-square tests. Factors associated with outcomes were assessed by Kaplan-Meier methods and multivariable Cox regression. **Results:** Median age, 63.7 years; 54.4% male. Primary site: 40% mucosal, 29% acral, 22% CSD, 9% others. Mut rate: 18% KIT, 16% BRAF, 14% NRAS, 52% wild-type (wt). Pathologic subtype differed by genetic subgroup ($p<.001$) while age, gender, and stage did not (all $p>0.05$). 18/26 (69%) KIT mut pts received imatinib in the metastatic (met) setting; 6/18 received $>$ 1 other KIT inhibitor. 3/25 (12%) BRAF mut pts received vemurafenib. 8/27 (30%) KIT mut, 4/27 (15%) BRAF mut, 6/20 (30%) NRAS mut, and 6/20 (30%) wt pts received ipilimumab. 149/180 (83%) pts developed mets at a median of 2.15 years (95% CI: 1.72, 2.72). Median follow-up (FU) of pts not developing mets was 3.91 yrs (range: 0.25, 14.34). Older age (HR: 1.02, 95% CI: 1.00, 1.03) and pathologic subtype (mucosal vs CSD HR: 1.70, 95% CI: 1.02, 2.84; non-CSD/ unknown vs CSD HR: 2.05, 95% CI: 1.00, 4.21) were associated with increased risk of mets but not with time from mets to death. Of 149 pts who progressed, 123 (83%) died during FU. Median time from met to death was 1.21 years (95% CI: 0.91, 1.67). Median FU from time of mets among those alive at last FU was 2.53 yrs (range: 0.06, 6.85). Mut status including KIT mut was not associated with time to first met or time from met to death. Pts who received ipilimumab from time of first distant met had reduced risk of death (HR: 0.55, 95% CI: 0.36, 0.87) independent of mut status. No impact was observed with KIT inhibition. **Conclusions:** KIT mut status is not an independent predictor of time to mets or survival in pts with mets. Ipilimumab improved pt outcomes regardless of mut status. The lack of impact of KIT inhibitors is likely due to the heterogeneity of KIT mut in mel but does not preclude efficacy in appropriately selected pts.

9050 General Poster Session (Board #45E), Sat, 8:00 AM-11:45 AM

Safety and efficacy of ipilimumab in melanoma patients who received prior immunotherapy on phase III study MDX010-020.

Howard Kaufman, Jose Lutzky, Joseph Clark, Kim Allyson Margolin, David H. Lawson, Asim Amin, Frances A. Collichio, Andrew Pecora, Walter John Urba, Kelly L. Bennett, David F. McDermott; Rush University Medical Center, Chicago, IL; Mount Sinai Comprehensive Cancer Center, Miami Beach, FL; Loyola University Medical Center, Maywood, IL; University of Washington, Seattle, WA; Emory University School of Medicine, Atlanta, GA; Levine Cancer Institute, Charlotte, NC; The University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC; Hackensack University Medical Center, Hackensack, NJ; Earle A. Chiles Research Institute-Providence Cancer Center, Portland, OR; Bristol-Myers Squibb, Plainsboro, NJ; Dana-Farber Cancer Institute, Boston, MA

Background: MDX010-020 was a phase III comparison of ipilimumab (Ipi), gp100 vaccine or the combination for advanced melanoma. A subset of patients (pts) received other immunotherapy (IM) for advanced disease prior to receiving Ipi, providing the opportunity to evaluate safety and efficacy of Ipi following IM. A prior analysis has shown that pts receiving prior IL-2 had a similar overall survival (OS) to pts who had not received prior IL-2 [Hodi et al *NEJM*2010]; we now report expanded results for pts receiving any prior IM (interferons and/or interleukin). **Methods:** Eligible pts (n=676) had unresectable stage III/IV melanoma and were randomized 3:1:1 to q3 wks x 4 doses of Ipi + gp100 or Ipi + placebo or gp100 + placebo. All Ipi doses were 3 mg/kg i.v. OS was retrospectively analyzed for pts receiving any prior IM; immune-related adverse events (irAEs) during induction were evaluated for pts who received any prior IM (322 pts, 48%) and for pts who received prior IL-2 (154 pts, 23%). **Results:** Demography and OS are summarized below. irAEs of any grade were reported for 60% (Ipi) and 54% (Ipi + gp100) of pts receiving any prior IM. Those receiving prior IL-2 specifically had 73% (Ipi) and 58% (Ipi + gp100) incidence of any grade irAEs. Incidence was similar for those not receiving prior IM or prior IL-2. Diarrhea, rash, and pruritus were the most common events in all groups. **Conclusions:** Results for OS in this subgroup analysis were similar for both those receiving any prior IM and those who did not receive prior IM and to the overall 020 population. In addition, safety profiles were similar irrespective of prior immunotherapy. Clinical trial information: NCT00094653.

	Ipi + gp100 n=403	Ipi + placebo n=137	gp100 + placebo n=136
N (%) receiving prior IM	194 (48%)	55 (40%)	73 (53%)
Male/female, %	66/34	66/34	55/45
Mean age (range), yrs	54 (24-78)	54 (24-78)	54 (23-79)
ECOG 0/1/2/3, %	59/39/1/1	60/40/0/0	58/40/3/0
Stage III/IV/M1c, %	2/98/73	2/98/73	1/99/74
Prior IM, OS hazard ratio (95% CI)		n=322	
Ipi vs gp100		0.54 (0.36, 0.82)	
Ipi + gp100 vs gp100		0.71 (0.53, 0.96)	
No prior IM, OS hazard ratio (95% CI)		n=354	
Ipi vs gp100		0.69 (0.48, 0.99)	
Ipi + gp100 vs gp100		0.66 (0.49, 0.90)	

9051 General Poster Session (Board #45F), Sat, 8:00 AM-11:45 AM

Melanoma of ocular, mucosal, and genital sites: Epidemiology and survival outcomes.

Kenneth D. Bishop, Adam J. Olszewski; Rhode Island Hospital, Providence, RI; Memorial Hospital of Rhode Island, Pawtucket, RI

Background: Melanomas arising from noncutaneous sites are rare entities with poorly defined staging, prognosis and no evidence-based treatment guidelines. **Methods:** We analyzed melanoma cases in the Surveillance, Epidemiology and End Results database between 1988 and 2007. Differences in clinical and pathologic features, treatment, and mortality were studied according to primary site of disease. The risk of melanoma-related death was calculated from life tables based on expected survival. Relative survival was compared in a multivariable parametric model using individual data. **Results:** We identified 209,861 cases of melanoma, of which 9,267 (4.4%) were noncutaneous. These were notable for older age, higher proportion of women, racial minorities, and advanced-stage disease. Mortality was high, even in subgroups with localized stage at diagnosis. Mucosal melanomas of the gastrointestinal and genitourinary tract had the highest excess mortality hazard ratios (HR) in the multivariate model. A substantial proportion of patients underwent organ-specific radical resection (32% eye enucleation, 40% radical head/neck surgery, 31% gastrectomy, 23% abdominoperineal resection). **Conclusions:** Melanoma arising from mucosal sites portends markedly worse prognosis than cutaneous melanoma. Prospective studies of systemic adjuvant treatment are needed for this disease, which is rarely curable even with aggressive local therapy.

Site	N	5-year risk of melanoma death	95%CI	Excess HR	95% CI	P value
Skin	200,594	10.0%	(9.8-10.2)	Reference		--
Eye	6,482	19.0%	(17.7-20.4)	1.19	(1.09-1.30)	0.0001
Nasal cavity	420	58.9%	(53.1-64.3)	1.42	(1.19-1.69)	0.0001
Sinuses	207	75.4%	(68.0-81.3)	1.86	(1.55-2.23)	<0.0001
Oral cavity	183	50.1%	(41.2-58.4)	1.25	(0.96-1.63)	0.1
Pharynx	41	81.3%	(66.4-90.1)	1.53	(1.03-2.28)	0.04
Stomach/esophagus	59	92.1%	(85.9-95.7)	3.58	(2.60-4.94)	<0.0001
Anus/rectum	491	75.5%	(70.9-79.4)	2.72	(2.39-3.09)	<0.0001
Urinary tract	46	67.7%	(51.3-79.6)	3.05	(1.94-4.79)	<0.0001
Vagina	281	79.6%	(73.9-84.1)	2.22	(1.87-2.63)	<0.0001
Vulva	741	40.9%	(36.5-45.2)	2.23	(1.93-2.57)	<0.0001
Male genitals	77	25.5%	(13.5-39.3)	0.89	(0.50-1.58)	0.69
Other sites	239	72.8%	(65.8-78.6)	2.29	(1.93-2.73)	<0.0001

9052 General Poster Session (Board #45G), Sat, 8:00 AM-11:45 AM

Pharmacodynamic effect of ipilimumab on absolute lymphocyte count (ALC) and association with overall survival in patients with advanced melanoma.

Michael Andrew Postow, Scott D. Chasalow, Jianda Yuan, Deborah Kuk, Katherine S. Panageas, Michael Cheng, Vafa Shahabi, David Mark Berman, Jedd D. Wolchok; Memorial Sloan-Kettering Cancer Center, New York, NY; Bristol-Myers Squibb, Princeton, NJ; Department of Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY; University of California, San Francisco, San Francisco, CA

Background: Ipilimumab (Ipi) is a fully human monoclonal antibody that augments antitumor T-cell responses. Ipi has been shown to improve overall survival (OS) in 2 phase (ph) III trials of advanced melanoma, as monotherapy at 3 mg/kg in previously treated patients (pts) (MDX010-20) or at 10 mg/kg with dacarbazine in previously untreated pts (CA184-024). In preclinical and clinical studies, inhibition of CTLA-4 by Ipi resulted in increases in activation and proliferation of peripheral T cells and increases in ALC. Baseline ALC may be a prognostic biomarker in several cancer types. The current analyses aim to increase understanding of changes in ALC with Ipi treatment and association of these changes with OS. **Methods:** Data were from 6 studies of Ipi with chemotherapy (CT) (ph I 078; N=59) or without CT (ph III MDX010-20; ph II trials 004, 007, 008, and 022; N=1203), and Ipi monotherapy in an Expanded Access Program (N=117) or with commercially available Ipi (N=71) or BRAF inhibitors (N=39). ALC was measured at baseline, prior to each dose during induction (weeks 1, 4, 7, and 10) and at the end of induction (week 13). Cox proportional hazards models were used to estimate and test associations between ALC measures and OS. **Results:** In all studies, mean ALC increased significantly over time in pts who received Ipi, with or without CT ($P<.0001$ to $P=.03$). There was no significant mean increase in ALC in pts who received gp100 or BRAF-inhibitor monotherapy. In study MDX010-20, pts with a greater rate of change in ALC from baseline to week 7 tended to have longer OS ($P=.0003$). A similar association was found between OS and ALC $\geq 1000/\mu L$ after 2 Ipi doses. However, pts in MDX010-20 had an OS benefit from Ipi relative to gp100, regardless of rate of change in ALC ($P=.14$). **Conclusions:** In these analyses, consistent with inhibition of CTLA-4, Ipi induced an increase in mean ALC, even with the addition of CT. A positive association between rate of ALC increase and OS was observed, but this was not specifically predictive of OS benefit from Ipi. Therefore, ALC cannot currently be used to guide clinical management with Ipi. However, further prospective investigation may be warranted.

9053 General Poster Session (Board #45H), Sat, 8:00 AM-11:45 AM

Long-term survival in patients with metastatic melanoma who received ipilimumab in four phase II trials.

Celeste Lebbé, Jeffrey S. Weber, Michele Maio, Bart Neyns, Kaan Harmankaya, Omid Hamid, Steven O'Day, Kevin M. Chin, Diane Opatt McDowell, Lori Cykowski, Brent McHenry, Jedd D. Wolchok; Hôpital Saint-Louis, Paris, France; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; UZ Brussel, Brussels, Belgium; Department of Dermatology, Division of General Dermatology, Medical University of Vienna, Vienna, Austria; The Angeles Clinic and Research Institute, Santa Monica, CA; The Beverly Hills Cancer Center, Beverly Hills, CA; Bristol-Myers Squibb, Wallingford, CT; Bristol-Myers Squibb, Lawrenceville, NJ; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Ipilimumab (Ipi) has shown improved overall survival (OS) in two phase III trials of patients (pts) with metastatic melanoma (MM), with survival follow-up of >4 years in one trial. The present analyses provide survival follow-up of >5 years in four phase II trials of Ipi in MM. **Methods:** Pts with MM were enrolled in one of four phase II trials: (1) CA184-004, a biomarker study with Ipi at 3 or 10 mg/kg in treatment-naive (TN) and previously treated (PT) pts; (2) CA184-007, with Ipi at 10 mg/kg +/- prophylactic budesonide in TN and PT pts; (3) CA184-008, a single-arm study with Ipi at 10 mg/kg in PT pts; and (4) CA184-022, a dose-ranging study of Ipi at 0.3, 3, or 10 mg/kg in PT pts (crossover from lower dose groups to 10 mg/kg was allowed upon disease progression). Ipi was administered q3 wk x4 (induction), followed by maintenance (q12 wk from week 24) in eligible pts. Some pts were retreated with Ipi at 10 mg/kg upon disease progression. Along with survival data collected through March 2012 for studies 007, 008, and 022, we report updated 5-year OS data for study 004 collected through September 2012. **Results:** Five-year OS rates for TN and PT pts are reported in studies 007, 008, and 022, with combined analyses for TN and PT pts within each dose group in study 004 (Table). The results show that survival rates reach a plateau beginning at year 3. **Conclusions:** In pts who received Ipi at 3 or 10 mg/kg in phase II studies, regardless of prior treatment, a proportion (12.3–49.5%) remained alive 5 years after the start of treatment. These results demonstrate long-term survival with Ipi therapy in MM. An ongoing phase III trial will compare OS for Ipi at 3 vs 10 mg/kg in pts with MM. Clinical trial information: NCT00162123.

Trial	N (prior Tx)	Ipi dose (mg/kg)	Median OS, months	OS rate, %				
				1-yr	2-yr	3-yr	4-yr	5-yr
004	42 (14 TN, 28 PT)	10	11.2	45.2	27.7	20.1	17.6	17.6
	40 (14 TN, 26 PT)	3	12.8	52.0	31.2	22.7	22.7	17.0
008	155 (PT)	10	10.2	47.2	32.8	23.3	19.7	18.2
022	72 (PT)	10	11.4	48.6	29.8	24.8	21.5	21.5
	72 (PT)	3	8.7	39.3	24.2	19.7	18.2	16.5
	73 (PT)	0.3	8.6	39.6	18.4	13.8	13.8	12.3
007	57 (total)	10 + placebo	19.3	62.4	41.8	34.4	32.0	32.0
	32 (TN)		30.5	71.4	56.6	42.5	37.7	37.7
	25 (PT)		14.8	50.8	24.2	24.2	24.2	24.2
	58 (total)	10 + budesonide	17.7	55.9	41.1	38.7	36.2	36.2
	21 (TN)		45.0	65.9	57.7	57.7	49.5	49.5
	37 (PT)		8.5	49.9	31.6	28.4	28.4	28.4

9054 General Poster Session (Board #46A), Sat, 8:00 AM-11:45 AM

Impact of age on treatment of primary melanoma patients.

Nathaniel H. Fleming, Jiaying Tian, Eleazar Vega-Saenz de Miera, Heidi L. Gold, Farbod Darvishian, Anna C. Pavlick, Russell S. Berman, Richard L. Shapiro, David Polsky, Iman Osman; New York University School of Medicine, New York, NY; Department of Pathology, New York University School of Medicine, New York, NY; Department of Medicine, NYU Langone Medical Center, New York, NY; Department of Surgery, New York University School of Medicine, New York, NY

Background: Although patient age at diagnosis is not currently included in guidelines for treatment of primary melanoma, several lines of evidence suggest that patient age is an important, yet understudied, factor when considering treatment options. Here, we attempt to address the limited knowledge of the impact of age on primary melanoma treatment. **Methods:** In a prospectively enrolled and followed-up cohort of melanoma patients at NYU, we used logistic regression models to evaluate the association between patient age at diagnosis, tumor baseline characteristics, including BRAF and NRAS mutation status, and likelihood of receiving and responding to adjuvant therapy. We examined adjuvant therapy effectiveness using recurrence and melanoma-specific survival as endpoints. **Results:** 444 primary melanoma patients were included in the study (median follow-up: 6.3 years; age range: 19-95 years). Age was categorized into three groups spanning the range of age at presentation: younger (19-45 years; 24%), middle (46-70 years; 50%), and older (71-95 years; 26%). Older patients were significantly more likely to have advanced stage, nodular subtype ($P < 0.01$, both variables), and BRAF wildtype tumors ($P = 0.04$). Controlling for these factors as well as gender, older patients experienced a higher risk of recurrence (HR older vs. younger 3.34, 95% CI 1.53-7.25; $P < 0.01$). Of the 128/444 (29%) patients who were eligible for adjuvant treatment (clinical stage $\geq$ IIB), only 67/128 (52%) received treatment. Using a propensity score that accounts for stage at presentation, patients in the middle age group were more likely to receive adjuvant therapy than those in the older group (OR 2.61, 95% CI 1.12-6.08; $P = 0.03$). In addition, a trend suggesting benefit from adjuvant therapy (defined as longer melanoma-specific survival) was observed only in the middle age group ($P = 0.07$). **Conclusions:** Our data suggest that older melanoma patients, despite having a significantly worse prognosis, are less likely to receive and benefit from adjuvant therapy. Further work is needed to understand the biological variables contributing to the limited response to treatment in elderly primary melanoma.

9055 General Poster Session (Board #46B), Sat, 8:00 AM-11:45 AM

Role of the immunoglobulin constant region in the antitumor activity of antibodies to cytotoxic T-lymphocyte antigen-4 (CTLA-4).

Alan J. Korman, John Engelhardt, Vafa Shahabi, Roumyana Yordanova, Karla Henning, Timothy Chen, Mark Selby; Bristol-Myers Squibb, Redwood City, CA; Bristol-Myers Squibb, Princeton, NJ

Background: Anti-CTLA-4 therapy enhances antitumor T-cell responses by both cell-intrinsic and cell-extrinsic mechanisms. Effector T-cell (Teff) activation is increased directly by interfering with CTLA-4-B7 interactions that negatively regulate T cells and by interfering with CTLA-4 expressed on regulatory T cells (Tregs), which function to inhibit immune responses. To analyze in greater detail the mechanism of action of anti-CTLA-4 antibodies (Abs), we examined the role of the immunoglobulin constant region in the antitumor activity of anti-CTLA-4 Abs in mouse tumor models. **Methods:** The activity of anti-CTLA-4 Abs with different mouse IgG constant regions were compared in several mouse tumor models, and intratumoral and peripheral T cells were analyzed by FACS. DNA samples from 488 patients with metastatic melanoma who received ipilimumab in a phase III clinical trial, MDX010-20, were analyzed for polymorphisms in the IgG fragment c receptor (FcR) at FCGR3A (V158F) and FCGR2A (H131R) loci. **Results:** In subcutaneous MC38 and CT26 colon tumor models, an anti-CTLA-4 Ab containing the mouse IgG2a constant region exhibited enhanced antitumor activity compared to an anti-CTLA-4 Ab containing the IgG2b constant region, while anti-CTLA-4 Abs containing mouse IgG1 or a mutated mouse IgG1 D265A constant region showed no activity. Anti-CTLA-4-IgG2a caused a dramatic reduction of Tregs at the tumor site that resulted in a greater Teff/Treg ratio. In contrast, all isotypes resulted in expansion of Tregs in the periphery. These results point to an important role for FcR in the action of anti-CTLA-4 Abs. In patients from study MDX010-20, there was no association between the 2 FcR polymorphisms (FCGR3A and FCGR2A) and overall survival. **Conclusions:** These preclinical studies reveal a novel dual activity of anti-CTLA-4 Abs consisting of intratumoral reduction of Tregs together with activation of Teff cells. This effect is mediated by the constant region and is presumably due to antibody-dependent cellular cytotoxicity. The data suggest that FcR-bearing cells at the tumor site, as well as the presence of intratumoral Tregs, may be important factors in the antitumor activity of anti-CTLA-4 Abs.

9056^ General Poster Session (Board #46C), Sat, 8:00 AM-11:45 AM

Safety and efficacy of adjuvant anti-PD1 therapy (nivolumab) in combination with vaccine in resected high-risk metastatic melanoma.

Geoffrey Thomas Gibney, Jeffrey S. Weber, Ragini Reiney Kudchadkar, Ronald C. De Conti, Leticia Tetteh, Cabell Eysmans, Bin Yu, Alberto J Martinez, Ibrahim Younos; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; Moffitt Cancer Center, Tampa, FL

Background: Nivolumab (BMS-936558), a fully human monoclonal antibody targeting the programmed death-1 (PD-1) receptor, has demonstrated clinical activity in advanced metastatic melanoma patients (pts). In this phase I study, the safety and activity of nivolumab plus a multipeptide vaccine was investigated as adjuvant therapy in resected stage IIIC and IV melanoma pts. **Methods:** HLA-A*0201 positive pts with HMB-45, NY-ESO-1, and/or MART-1 positive tumors received nivolumab (1mg/kg, 3mg/kg, or 10mg/kg IV) with a multipeptide vaccine (gp100, MART-1, NY-ESO-1, Montanide ISA 51 VG) every 2 weeks for 12 doses followed by nivolumab maintenance every 3 months (8 doses) or until disease recurrence. The primary objective was safety and determination of maximum tolerated dose (MTD). Secondary objectives were immunologic response and relapse free survival. **Results:** 33 pts were enrolled: 12 pts at 1mg/kg, 10 pts at 3mg/kg, and 11 pts at 10mg/kg nivolumab. Median age was 47 yrs; 55% male and 52% M1c disease (2 IIIc, 7 M1a, 7 M1b, and 17 M1c pts). As of January 16, 2012, median follow up time was 14 months and median number of doses was 12 (20 pts still receiving therapy). A MTD was not reached. Grade 2-3 related adverse events (AEs) occurred in 27 pts with the most common AEs being fatigue, rash/pruritis, and endocrinopathies. 4 pts experienced grade 3 AEs: (colitis/diarrhea (3), rash (1)). No drug related grade 4 or higher AEs occurred. 7/33 pts have relapsed to date. One pt with biopsy-proven relapse on trial had spontaneous disease regression. Non-relapsing pts had higher pre-treatment PD-1 expression on T_{reg} and T_{CD4+} cells ($p=0.053$) and a greater increase in T_{reg} cells after 12 weeks on treatment ($p=0.027$). Among all pts, treatment led to a rise in T_{reg} cells ($p=0.015$) and decreased PD-1 expression on T_{CD4+} and T_{CD8+}cells ($p=0.014$ and $p<0.001$, respectively). **Conclusions:** Nivolumab is well tolerated in combination with vaccine and preliminary data demonstrates immunologic and clinical activity as adjuvant therapy, justifying a randomized phase III study in resected high risk melanoma pts. Clinical trial information: NCT01176474.

9057 **General Poster Session (Board #46D), Sat, 8:00 AM-11:45 AM**

BEVATEM: Phase II study of bevacizumab (B) in combination with temozolomide (T) in patients (pts) with first-line metastatic uveal melanoma (MUM): Final results.

Sophie Piperno-Neumann, Vincent Servois, Francois-Clement Bidard, Pascale Mariani, Corine Plancher, Alhassane Diallo, Nora Vago-Ady, Laurence Desjardins; Institut Curie, Paris, France; Roche France, Boulogne Billancourt, France

Background: Overall survival (OS) of MUM pts remains poor (median 12 months), stressing the lack of effective therapies in this rare cancer. Targeting angiogenesis seems to be promising in uveal melanoma (UM). Antiangiogenic agents are used to treat neovascular ocular diseases such as age-related macular degeneration or proliferative diabetic retinopathy. B suppressed in vitro growth and in vivo hepatic establishment of micrometastases in experimental UM. Preclinical data suggest a potential clinical benefit of the combination of dacarbazine and B. **Methods:** Two-stage phase II trial; expected 6-month progression-free rate (PFR) of 40% with BEVATEM versus 15% with chemotherapy (power 94%, α risk 3%). Primary endpoint: 6-month PFR according to RECIST. Secondary objectives: response and survival rates, safety; liver perfusion CT for functional imaging of response; impact of VEGF-A gene polymorphisms on B pharmacodynamics. Treatment schedule: T 150mg/m2 d1-d7 and d15-d21 oral route, B 10 mg/kg d8 d22 IV infusion, 6 cycles (d1=d28) then B maintenance until toxicity or progression. **Results:** 35 evaluable pts have been enrolled from May 2010 to May 2012. First step analysis showed 3/17 first patients with disease control at 6 months and good tolerance. The final population consisted of 19 men and 16 women, median age 55 (29-72). PS was 0 in 28 and 1 in 7 pts, and the median time to metastasis was 38 months (17-62). Liver was the sole metastatic site in 29 pts.With an administered dose-intensity similar to the planned schedule, 7 and 9 pts experienced grade 3 (neutropenia 4, thrombocytopenia 1, constipation 1, pruritis 1) or grade 4 toxicities (neutropenia 3, thrombocytopenia 4, thrombosis 1) respectively. Despite no objective response, 9/35 pts showed stable disease, and the 6-month PFR was 26% [95%CI 13-41]. With a median follow-up of 18 months, 5 pts (14%) had long lasting non progressive disease with B maintenance (10+ to 29+ months). Finally, the median PFS and OS were 3 and 12 months respectively. **Conclusions:** BEVATEM regimen in first line MUM patients showed safety and 6-month PFR of 26% including 14% of pts with durable clinical benefit. Clinical trial information: 2009-011751-46.

9058 General Poster Session (Board #46E), Sat, 8:00 AM-11:45 AM

Analysis of serum biomarkers and tumor genetic alterations from a phase II study of lenvatinib in patients with advanced BRAF wild-type melanoma.

Pallavi Sachdev, Omid Hamid, Kevin Kim, Axel Hauschild, Steven O'Day, Corina Andresen, Yasuhiro Funahashi, Tadashi Kadowaki, James P. O'Brien, Keith Flaherty; Eisai Inc., Woodcliff Lake, NJ; The Angeles Clinic and Research Institute, Los Angeles, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Universitätsklinikum Schleswig-Holstein, Kiel, Germany; The Beverly Hills Cancer Center, Beverly Hills, CA; Eisai Inc., Andover, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Lenvatinib is an oral receptor tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFRβ. Phase I and II studies of lenvatinib demonstrate that a subset of advanced melanoma patients (pts) appears to derive benefit from lenvatinib treatment (tx), prompting a need to identify predictive biomarkers for response to lenvatinib. **Methods:** Serum and archival tumor samples were collected from 93 enrolled pts in the BRAF wild-type (wt) cohort of the lenvatinib phase II study of advanced melanoma. Concentrations of 50 factors were measured in pre- and post-tx serum samples; 58 archival tumor tissues were obtained and gene mutation (mut) (n=53) and gene expression profiling (GEP) (n=39) analyses were performed. For mut analysis, targeted resequencing was performed on a select panel of genes using the Ion PGM Sequencer and mut validation studies were performed. For GEP analysis, the nCounterAnalysis System was used to measure the expression level of 330 genes. **Results:** Clinical benefit rate (32%) and objective response rate (9%) by independent radiologic review were observed in the BRAF wt cohort. In serum biomarker analysis, lenvatinib tx resulted in a decrease in soluble VEGFR2 and increase in VEGF and PlGF levels consistent with target engagement. Correlation with clinical outcome demonstrated that baseline (BL) levels of Ang-2, IL8, PlGF, and PDGFBB associated with OS, but only pts with low BL Ang-2 levels also demonstrated improved response. High BL levels of FLT3LG and eotaxin associated with longer OS and improved response. In GEP analysis, expression levels of a set of genes including TARBP2, ZNF544, and NF1 (targets identified in phase I and preclinical studies) associated with OS. In gene mut analysis, NRAS mut showed a trend towards longer OS. Pts with NRAS mut along with wt PIK3CA status demonstrated longer OS. **Conclusions:** Lenvatinib demonstrated limited response in BRAF wt advanced melanoma pts. A subset of pts may derive extended clinical benefit. NRAS mut/PIK3CA wt status and low BL Ang-2 levels appear to associate with improved clinical outcome in this pt population and require further study to assess their predictive value. Clinical trial information: NCT01136967.

9059 **General Poster Session (Board #46F), Sat, 8:00 AM-11:45 AM**

Ipilimumab (Ipi) retreatment at 10 mg/kg in patients with metastatic melanoma previously treated in phase II trials.

Bart Neyns, Jeffrey S. Weber, Celeste Lebbé, Michele Maio, Kaan Harmankaya, Omid Hamid, Steven O'Day, Kevin M. Chin, Diane Opatt McDowell, Lori Cykowski, Brent McHenry, Jedd D. Wolchok; UZ Brussel, Brussels, Belgium; Moffitt Cancer Center, Comprehensive Melanoma Research Center, Tampa, FL; Hôpital Saint-Louis, Paris, France; University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; Department of Dermatology, Division of General Dermatology, Medical University of Vienna, Vienna, Austria; The Angeles Clinic and Research Institute, Los Angeles, CA; The Beverly Hills Cancer Center, Beverly Hills, CA; Bristol-Myers Squibb, Wallingford, CT; Bristol-Myers Squibb, Lawrenceville, NJ; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Ipi is a fully human monoclonal antibody that binds to cytotoxic T-lymphocyte antigen-4 to augment antitumor immune responses. In phase III study MDX010-20, where patients (pts) could be retreated if they met safety criteria and achieved an objective response or stable disease ≥3 months from the end of the induction period (q3 weeks for 4 doses), 21 of 31 pts (68%) retreated with Ipi reestablished disease control. CA184-025 is a roll-over study of extended Ipi treatment or survival follow-up in pts who received Ipi in phase II trials, with the primary objective of evaluating safety during extended treatment. We report the safety profile in pts retreated with Ipi in study 025. **Methods:** Eligible pts in phase II trials CA184-004, -007, -008, -022, MDX010-08, or -015 were enrolled in study 025 (N=248) to receive retreatment (at the time of progression), extended maintenance (if no prior progression), or survival follow-up only. Pts were ineligible for retreatment if they had experienced a grade 3-4 non-skin toxicity during prior Ipi therapy. Ipi was administered at 10 mg/kg, q3 weeks for 4 doses, to 111 pts who initially received Ipi induction at 0.3, 3, or 10 mg/kg in a parent study. **Results:** In this selected population of eligible pts, the nature and frequency of immune-related adverse events (irAEs) during retreatment were similar to those reported in previous studies, which most commonly affected the GI tract and skin (Table). There were no new types of drug-related irAEs and no grade 5 irAEs upon retreatment. **Conclusions:** Retreatment with Ipi at 10 mg/kg in these pts was generally well tolerated and the safety profile was similar to that during induction dosing in the parent studies. The higher frequencies of irAEs at lower doses should be interpreted with caution given the small sample sizes. An ongoing, randomized phase II trial will evaluate the clinical benefit of Ipi retreatment. Clinical trial information: NCT00162123.

	Ipi dose in parent study with retreatment at 10 mg/kg, n (%)		
irAEs	**0.3 mg/kg, n=24**	**3 mg/kg, n=34**	**10 mg/kg, n=53**
Any grade	18 (75.0)	23 (67.6)	30 (56.6)
Grade 3-4	6 (25.0)	2 (5.9)	7 (13.2)
GI grade 3-4	3 (12.5)	1 (2.9)	2 (3.8)
Skin grade 3-4	1 (4.2)	1 (2.9)	2 (3.8)
Liver grade 3-4	1 (4.2)	0 (0.0)	2 (3.8)
Endocrine grade 3-4	1 (4.2)	0 (0.0)	1 (1.9)

9060 General Poster Session (Board #46G), Sat, 8:00 AM-11:45 AM

Vemurafenib (VEM) in patients (pts) with BRAF-mutant melanoma and brain metastases (mets).

James J. Harding, Federica Catalanotti, Amin Yaqubie, Gregory C. McDermott, Romona Kersellius, Taha Merghoub, Richard D. Carvajal, Sandra P. D'Angelo, Mark Andrew Dickson, Gary K. Schwartz, Jedd D. Wolchok, Michael F. Berger, David B. Solit, Paul B. Chapman; Memorial Sloan-Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY; New York-Presbyterian Hospital, New York, NY

Background: Emerging data suggest that RAF inhibitors are an effective therapy for pts with BRAF-mutant melanoma and brain mets. Although reported efficacy is encouraging, these data are derived from case reports or early stage trials enriched with physiologically fit pts. It is therefore of interest to assess the "real world" experience of VEM in this population. **Methods:** Records of all BRAF-mutant melanoma pts treated with RAF inhibitors at our center from 2007 to 2012 were reviewed retrospectively. We determined the best overall response rate (BORR) and, when applicable, the overrall intracranial response rate (OIRR) by RECIST v1.1, progression-free survival (PFS), and overall survival (OS) to RAF inhibition. Pretreatment formalin-fixed, paraffin-embedded tumor was assessed using an exon capture assay able to sequence coding exons of 279 cancer-associated genes. **Results:** 21 (18%) of 119 pts with BRAF-mutant melanoma treated with VEM had active brain mets (age range: 25-86, sex: 52% men, median ECOG PS: 1, proportion with extracranial mets: 90%, BRAF mutation: 86% V600E and 14% V600K). 10/21 pts had no prior intracranial (IC) therapy; 11/21 pts received whole brain radiotherapy (WBRT, 7/21), stereotactic radiosurgery (1/21), metastasectomy (2/21) or multimodality therapy (1/21) prior to VEM. 12/21 pts received ipilimumab sometime during their disease course. For radiographically evaluable pts (N=17), the BORR was 65% (95% CI: 43-88) and the OIRR was 40% (95% CI: 15-65). For 4 pts, the BORR and OIRR were discordant−3 pts had IC progression but visceral tumor shrinkage, 1 pt had IC disease control but visceral progression. VEM was effective in pts whether or not they had received prior local brain therapy. The estimated median PFS and OS for all brain mets pts (N=21) were 4 and 8 months, respectively. Pretreatment tumor is available for exon sequencing in approximately half of these patients. This analysis is ongoing. **Conclusions:** In routine clinical practice, the OIRR to VEM was 40% which is higher than historical response rates to WBRT. VEM may be preferable to WBRT as a first-line therapy for pts with BRAF-mutant melanoma and brain mets. Whether RAF inhibitor treatment improves OS in this population will require further study.

9061 General Poster Session (Board #46H), Sat, 8:00 AM-11:45 AM

Health behaviors and survivorship needs of short- versus long-term melanoma survivors.

Susan M. Swetter, Arianna Aldridge Gerry, Kelly Bugos, Ralph Steven Greco, Katherine L. McGurk, Oxana Palesh; VA Palo Alto Health Care System; Stanford University Medical Center, Stanford, CA; Stanford University, School of Medicine, Stanford, CA; Stanford University Medical Center, Stanford, CA

Background: Little is known about melanoma survivors and their long-term symptoms, sun protection practices and support needs from health professionals. **Methods:** Melanoma survivors previously treated at Stanford Cancer Center completed a quality improvement survey to explore the value of a melanoma survivorship clinic, as part of the Stanford Cancer Survivorship Program. The survey period ranged from July 2012 to September 2012, and 17% of the 893 invited survivors responded. We compared responses of melanoma survivors diagnosed between 2006-2011 (short-term) and 1995-2005 (long-term). **Results:** 153 cancer survivors (41% short- and 59% long-term) completed the survey. On average, they were 62 years of age (SD=15.1), 94% Caucasian, 47% female, and 68% underwent local excision alone. Long- vs. short-term survivors were less likely to receive routine skin screening every 3-6 months (38% vs. 83%, $p<0.001$) or follow-up for their melanoma in the last 6 months (54% vs. 76% $p=0.045$). Sun protection practices were similar between groups; however, long-term survivors decreased their use of tanning beds (33% vs. 18%, $p=0.03$) and time seeking a tan relative to short-term survivors (72% vs. 48%, $p=0.002$). Overall, survivors rated anxiety as the most prevalent symptom (33%), followed by numbness of the scar site (31%), forgetfulness (26%), sleep problems and depression (23%), pain and fatigue (17%). Sixty-eight percent of all survivors reported their symptoms were not addressed by their health provider, and of those stating their provider addressed their symptoms (32%), the survivor initiated the conversation 71% of the time. In general, survivors desired education about the long-term effects of melanoma (41%), family risk of skin cancer (28%), and protecting their skin from further damage (20%). Twenty percent of all survivors requested treatment for the long term effects of melanoma, and 12% wanted emotional support. **Conclusions:** Melanoma survivors experience continuing symptoms long after treatment, namely anxiety, and express a need for information about long-term melanoma effects, psychosocial support, and prevention of further skin cancer. Clinicians should routinely assess survivorship needs to improve quality of life.

9062 General Poster Session (Board #47A), Sat, 8:00 AM-11:45 AM

Clinical characteristics and survival of BRAF-mutant (BRAF+) metastatic melanoma patients (pts) treated with BRAF inhibitor (BRAFi) dabrafenib or vemurafenib beyond disease progression (PD).

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Background: Accelerated tumor growth has been demonstrated on BRAFi cessation in BRAFi-resistant melanoma cell lines. In BRAFi-treated pts initial response rates are high but most have PD at 6+ months. The benefit of ongoing BRAFi after PD is unknown. We sought to describe the characteristics of pts treated beyond progression (TBP) vs those not TBP, and whether TBP prolongs survival. **Methods:** Clinicopathologic data were collected on 112 pts enrolled in phase I-IV clinical trials at Westmead Hospital and Melanoma Institute Australia from July 2009 to Sept 2012 with unresectable stage IIIC or IV BRAF+ melanoma treated with single agent dabrafenib or vemurafenib. TBP was defined as ongoing BRAFi >28 days beyond RECIST PD. Pt and disease characteristics at baseline and at PD were examined, as well as survival data. **Results:** 92/112 (82%) pts had RECIST PD. 36/92 (39%) pts were TBP (mean 144 days, median 93 days, range 29–572 days). Pts TBP were significantly more likely to have achieved a RECIST response (CR/PR) prior to PD, have a lower ECOG at PD, presence of brain metastases at PD, have PD treated locally and a smaller RECIST sum of diameters (SoD) at PD, compared with those not TBP (all $p<0.05$). Median OS from commencement of BRAFi in those TBP was longer than those not TBP (15.0 vs 6.5 months, $p<0.001$), as was OS from RECIST PD (7.4 vs 1.9 mo, $p=0.001$). In multivariate analysis of all pts, TBP improved OS from RECIST PD (HR 0.32, $p=0.012$) even after adjusting for other potential prognostic factors at PD (see table). Within the TBP cohort, RECIST SoD at PD was the only factor that influenced OS from PD ($p=0.009$), and presence of brain metastases did not. **Conclusions:** Treatment with BRAFi may be continued after RECIST PD in selected pts, and is associated with a prolonged OS compared with ceasing treatment at PD.

Factors at progression	Hazard ratio	95% CI	P value
TBP	0.32	0.13-0.78	0.012
SoD at PD (mm)	1.005	1.001-1.009	0.009
Brain metastasis present	2.79	1.13-6.89	0.026
ECOG (>1)	1.13	0.56-2.25	0.736
LDH (>ULN)	1.98	0.74-5.33	0.176
PD treated locally	0.97	0.38-2.49	0.952

LDH; lactate dehydrogenase; ULN; upper limit of normal.

9063 General Poster Session (Board #47B), Sat, 8:00 AM-11:45 AM

Evaluating the safety of anti-CTLA-4 therapy in the elderly with unresectable melanoma.

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Background: Anti-CTLA-4 monoclonal antibodies demonstrated an improvement in overall survival in patients with metastatic melanoma and ipilimumab (ipi) was FDA approved in 2011. We performed a retrospective analysis of 74 elderly (age $\geq$ 65) patients (pts) who were treated with anti-CTLA-4 therapy (tx) and evaluated their treatment related adverse events (AEs) as well as clinical response. **Methods:** 65 pts were treated with ipi 3 mg/kg x 4, among whom 8 pts were re-treated with ipi 3 mg/kg x 4; 3 pts were treated with ipi 10 mg/kg x 4 with 2 pts who went on to receive maintenance tx; 2 pts were treated with tremelimumab (treme) 15 mg/kg q 3 months; 4 pts are currently undergoing tx with ipi 3 mg/kg x 4. There were 17 treatment naïve pts, and 57 pts were previously treated with 1-4 prior therapies. Thirty-nine pts received all 4 doses of ipi. There were 46 males and 28 females. Ages ranged from 65 to 90, median age 74. Melanoma subtypes included: 55 cutaneous, 8 mucosal, 7 ocular, 3 acral, and 1 unknown primary. Ten pts had M1a, 18 M1b, and 45 M1c disease. One pt had unresectable stage IIIC disease. **Results:** The most common tx related AEs included rash (33 AEs $\leq$ grade 3), diarrhea/colitis (21 AEs $\leq$ grade 3, with 1 grade 4 AE), fatigue (17 AEs $\leq$ grade 2), and pain at tumor site (17 AEs $\leq$ grade 2). There were 3 hepatotoxicity-related AEs, including 1 grade 5 AE; and 3 endocrinopathy-related AEs, including 1 grade 4 hypopituitarism. Toxicities were managed with corticosteroids, anti-histamines, anti-motility agents, analgesics, thyroid and cortisol supplementation. Of the 69 pts evaluable for response, 16 pts (23%) had complete response (CR) or partial response (PR), and 9 pts (13%) had stable disease (SD) as measured radiographically using mWHO criteria at least 12 weeks post completion of treatment. When analyzed within melanoma subtypes, 17 cutaneous pts (31%) had tumor response (CR, PR, SD), 6 mucosal (75%), and 2 ocular (29%). **Conclusions:** Anti-CTLA-4 tx, including ipi and treme, was safe and well tolerated by the elderly population. Reported adverse events and response rates were consistent with published data in younger cohorts.

9064 General Poster Session (Board #47C), Sat, 8:00 AM-11:45 AM

Survival patterns following brain metastases for patients with melanoma in the targeted therapy era.

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Background: Survival from metastatic melanoma (MM) has been significantly prolonged with the introduction of molecularly targeted therapy, including BRAF inhibitors (BRAFi) for patients (pts) with the V600E mutation. Here, we present the first data describing patterns of survival after diagnosis of brain metastases (BM) in a large cohort of these pts with long follow-up. **Methods:** A retrospective review of 191 MM pts accrued on multiple prospective trials between 2008–2012 was conducted. These trials assessed novel immunologic and targeted therapies in pts with both BRAF mutant (n=70) and wild type/unknown (n=121) tumors. We evaluated pt characteristics and the impact of systemic and BM-directed treatments. **Results:** Of 98 pts who developed BM, median follow-up after first BM was 7.7 months (15.5 months for the 25 living pts), and 33 were treated with BRAFi. Median duration of BRAFi use was 5.9 months (range 0.7–27.1), which preceded BM in 30%, was concurrent with first BM in 18%, and followed first BM in 52%. Ipilimumab or anti–PD-1/PD-L1 immunotherapy was given to 58% of pts who received a BRAFi and 95% of those who did not. Limited intracranial disease on initial BM presentation (defined as ≤3 lesions) occurred in 70% of BRAFi-treated pts and 74% of non-BRAFi pts, and 70% of BRAFi pts received at least one focal BM treatment (stereotactic radiosurgery or resection) compared to 75% of non-BRAFi pts. As shown in the Table, actuarial survival after BM diagnosis was prolonged among pts treated with a BRAFi. This is due primarily to the nearly 2-year median survival of pts for whom a BRAFi was initiated after BM were diagnosed. **Conclusions:** Survival for pts with BM from BRAF mutant MM can significantly exceed the often anticipated 4–6 months, particularly if a BRAFi is initiated after BM arise. This supports BRAFi activity in intracranial disease, and helps to inform trials currently under way testing BRAFi use among MM pts with previously diagnosed BM.

	Median survival, months (95% CI)	Number of pts	
BRAF mutant, with BRAFi	13.2 (7.6 – 23.2)	33	
BRAFi started pre-BM	5.6 (0.8 – 14.1)	16	Log-rank p = 0.02
BRAFi started post-BM	23.2 (10.2 – 27.8)	17	
BRAF mutant, no BRAFi	6.7 (2.3 – 12.1)	7	
BRAF wild type	8.0 (5.6 – 21.0)	34	
BRAF unknown	6.5 (3.5 – 9.4)	24	

9065 General Poster Session (Board #47D), Sat, 8:00 AM-11:45 AM

Correlation between efficacy and toxicity in pts with pretreated advanced melanoma treated within the Italian cohort of the ipilimumab expanded access programme (EAP).

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Background: Ipilimumab was the first agent approved for the treatment of unresectable or metastatic melanoma that showed an overall survival benefit in randomised phase III trials. Early clinical studies explored the potential relationship between immune-related adverse events (irAEs) associated with ipilimumab and antitumor activity but no definitive conclusion has been reached. Here, we evaluated the possible correlation between efficacy of ipilimumab treatment and irAEs in patients (pts) enrolled in the EAP in Italy. **Methods:** Ipilimumab was available upon physician request for pts aged ≥16 years with unresectable stage III/stage IV melanoma who had either failed systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Pts were monitored for adverse events (AEs), including immune-related AEs (irAEs), using Common Terminology Criteria for Adverse Events v.3.0. **Results:** In total, 855 Italian pts participated in the EAP from June 2010 to April 2012 across 55 centres. Among 833 evaluable pts, 278 pts (33.4%) reported an irAE and 555 (66.6%) did not. As of December 2012, the disease control rates among pts with or without irAEs were 35.3% and 33.9% respectively. We noted that there was a difference in the distribution of pts with or without irAEs among pts who experienced a fast progression, thus not being able to receive at least 3 cycles, and pts with slow progression. In fact, due to the mechanism of action of the drug and consequent delayed onset of irAEs, pts with irAEs among fast and slow progressors were 22% and 37% respectively. Therefore, median overall survival was evaluated by adjusting the 2 groups for this factor and results showed a comparable survival between pts who reported an irAE and pts who did not (10.0 vs 9.7 months respectively). **Conclusions:** This exploratory analysis of EAP data suggest that activity and efficacy of ipilimumab is not related with the occurrence of irAEs.

9066 General Poster Session (Board #47E), Sat, 8:00 AM-11:45 AM

Efficacy, safety, and pharmacokinetics (PK) of the BRAF inhibitor dabrafenib (D) hydroxypropyl methylcellulose (HPMC) capsule formulation in combination with the MEK1/2 inhibitor trametinib (T) in patients (pts) with BRAF mutation-positive metastatic melanoma (MM).

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Background: Preclinical studies ofD + T show enhanced activity in BRAF mutant MM vs either drug alone. D + T safety and efficacy were evaluated in a 4-part (A–D) phase I/II study. Part D assessed the impact on efficacy, safety and PK of a more stable HPMC capsule formulation of D alone, and in combination with T, instead of the gelatin capsule used in Parts A–C. **Methods:** 110BRAF$^{V600E/K}$MM pts with RECIST measurable disease were randomized to 4 cohorts. Dose-limiting toxicities (DLTs) were evaluated for the first 3 weeks of treatment. PK sampling was done on Days 1 and 21. Primary endpoints were PK and safety; secondary endpoints were response rate (RR) and overall survival (OS). **Results:** Median age was 54 years, 58% male, 65% ECOG PS 0, 88% V600E, 68% M1c stage, 97% no prior brain metastases, and 45% LDH > ULN. Treatment (tx) with D HPMC + T had little impact on ratio of D C_{max} (1.16) and D AUC (1.23) vs D tx alone; but led to higher ratio of D C_{max}(1.51) but similar D AUC (1.10) vs D gelatin + T seen in Part B. Median progression-free survival (PFS) and RR are in Table. Median PFS not reached in D4. No DLTs occurred in the first 15 subjects enrolled in D4. Most common AEs (≥40%) for all cohorts were pyrexia, nausea, chills, vomiting, arthralgia, and fatigue. Most common grade >3 AEs (all 5%) were hypertension, pyrexia, increased GGT, and hyponatremia. 11% of pts discontinued treatment due to an AE. There were no major differences in toxicities between cohorts and Parts A–C. **Conclusions:** The D + T combination had an acceptable safety profile with clinically manageable side effects. D HPMC + T had little impact on D C_{max} and D AUC vs D alone. D HPMC led to higher D C_{max}but similar D AUC vs gelatin + T. Meaningful clinical activity was seen in all dose combinations with D HPMC +T; PFS, RR, and duration of response were consistent with other study parts. Phase 3 studies with D HPMC + T are ongoing. Clinical trial information: NCT01072175.

Part D dabrafenib HPMC dose cohorts.

Cohort	Dabrafenib dose (mg BID)	Trametinib dose (mg QD)	N	Median PFS (months)	RR (%)
D1	75	2 (starting Wk 4)	12	6.9	67
D2	150	2 (starting Wk 4)	16	9.3	69
D3	75	2	43	7.5	74
D4	150	2	39	NR	67

9067 General Poster Session (Board #47F), Sat, 8:00 AM-11:45 AM

The clinical and biologic impact of PPP6C mutations in melanoma.

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Background: PP6C binds to regulatory units to affect a number of important pathways including cell proliferation and DNA repair. Recently two independent groups reported for the first time the presence of somatic mutations in the PPP6C gene in ~10% of short term cultures and limited number of human melanoma tissues. However, the clinical or biological relevance of PPP6C mutations in melanoma patients is unknown. Our objectives were to examine the clinical relevance of PPP6C mutations in a well characterized cohort of melanoma specimens linked to extensive, prospectively-collected clinical information and to explore the functional consequence of different categories of mutations. **Methods:** Sanger dideoxy sequencing was performed on PCR-amplified DNA from macro-dissected FFPE tumors. Associations between PPP6C mutations and baseline characteristics, recurrence, survival, and BRAF/ NRAS mutational status were examined. The impact of mutations on binding PP6C regulatory units was assessed as well as the effect on additional downstream pathways. **Results:** 308 primary melanoma patients (118 Stage I, 92 Stage II, and 98 Stage III) were examined (median follow up: 5.3 years). 50 PPP6C mutations in 33 patients (10.7%) were identified with 11 tumors harboring more than one mutation. One mutation (R301C) was identified in 6 patients. PPP6C mutations occurred with similar frequencies across stages and showed no association with BRAF or NRAS mutations. Mutations were categorized into 3 groups: Mutations resulting in premature stop codon (n=9), those occurring in the active site (n=16) and others (n=8). 8/9 (89%) patients with stop mutations recurred and developed visceral metastases. Functional studies revealed that PPP6C mutants also behaved differently; some PPP6C mutations led to decreased binding to regulatory subunits, others, including the R301C mutation did not. **Conclusions:** Our data suggest that PPP6C mutation is an early event in melanoma progression and independent of BRAF or NRAS mutations. Data also suggest different biologic and clinical impact of PPP6C mutations, with stop mutations showing association with development of visceral metastases that requires further clinical and functional study.

9068 General Poster Session (Board #47G), Sat, 8:00 AM-11:45 AM

DOC-MEK: A double-blind randomized phase II trial of docetaxel with or without selumetinib (AZD6244; ARRY-142886) in wt *BRAF* advanced melanoma.

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Background: Inhibitors of mutant BRAF have transformed the treatment of melanoma for the 40% of patients whose tumors harbor V600 mutations. ERK1/2 is constitutively active in melanoma cells regardless of mutation status, and plays key roles in cell cycle entry, invasion, angiogenesis and in resistance to apoptosis. Selumetinib is a highly selective allosteric inhibitor of MEK1/2, suppressing pERK levels in melanoma independent of BRAF and NRAS mutation status. In melanoma cells, docetaxel induces mitochondrial dependent apoptosis by activation of Bax. Activation of ERK1/2 results in degradation of the BH3-only protein Bim and phosphorylation of Bad, inhibiting apoptosis. Selumetinib and docetaxel have demonstrated synergy in a variety of xenograft models, including melanoma. **Methods:** DOC-MEK (NCT01256359) is a randomised, double-blind, placebo-controlled multi-centre study in patients with wild-type BRAF advanced melanoma. Patients were randomised (1:1) to docetaxel with placebo or selumetinib, with stratification for M stage and performance status. Docetaxel was administered intravenously every 3 weeks at a dose of 75mg/m^2 for a maximum 6 cycles. Placebo or selumetinib 75mg was given orally twice per day until disease progression or unacceptable toxicity. **Results:** Between October 2010 and April 2012 eighty three patients were randomised at 18 sites from 257 patients screened. Progression free survival (PFS) favored combination therapy (HR 0.753, p=0.13), as did response rate (32 vs 14%, p=0.059) and 6 month PFS (40 vs 26%, p=0.19). Patients on docetaxel with selumetinib experienced more rash, diarrhea, febrile neutropenia and edema, but less neuropathy. Overall survival data and outcomes according to tumor NRAS mutation status will be presented. **Conclusions:** Although PFS and response rates favored docetaxel with selumetinib further interest in the regimen will be dependent on overall survival outcomes and/or the identification of a sub-population that benefit most from this approach. Clinical trial information: NCT01256359.

9069 **General Poster Session (Board #47H), Sat, 8:00 AM-11:45 AM**

Personal melanoma risk awareness versus intrinsic risk.

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Background: Intrinsic risk factors for melanoma include personal and family history of the condition, a high number of naevi and a light skin phototype (I or II). The objective of this study was to evaluate the correlation between personal awareness of melanoma risk and objective risk factors and to analyze the elements associated with under-or over-evaluation of the actual risk. **Methods:** EDIFICE melanoma, a nationwide French observational survey, was conducted through phone interviews on a representative sample of 1502 subjects aged $\geq$ 18 using typical quotas. The survey took place from 28th Sept 2011 to 20th Oct 2011. **Results:** 393 subjects (26%) had at least one melanoma risk factor: personal: 1%; family history: 11%; high number of naevi: 8% and phototype I-II: 11%. 1109 (74%) had no risk factor. 1029 (73%) had a correct perception of their risk level, 135 (10%) overestimated their risk and 241 (17%) underestimated it. Compared to the control group (correct perception), the population overestimating the melanoma risk is characterised by a higher percentage of individuals living alone (32% vs. 24%, $p<0.05$), socio-professional category + (38% vs. 28%, $p<0.01$) and greater alcohol consumption (45% vs. 34%, $p<0.02$). They are also more likely to expose themselves to the sun (89% vs. 78%, $p<0.004$) and less likely to use sunscreen protection (58% vs. 44%, $p<0.003$). A greater proportion of them participates in melanoma screening programmes (21% vs. 14%, $p<0.04$). The population that underestimates the risk is characterised by lower educational attainment (11% vs. 7%, $p<0.05$), greater use of high SPF sunscreen (41% vs. 29%, $p<0.0004$) and a more frequent use of UV sunbeds (9% vs. 6%, $p<0.06$). **Conclusions:** Overall, the French have a fair perception of their personal likelihood of developing melanoma. Interestingly, subjects overestimating their intrinsic risk do not behave appropriately with respect to sun protection measures (more sun exposure and less sunscreen protection). On the other hand, subjects underestimating their risk use UV sunbeds more extensively.

9070 General Poster Session (Board #48A), Sat, 8:00 AM-11:45 AM

Italian cohort of ipilimumab expanded access programme (EAP): Efficacy, safety, and correlation with mutation status in metastatic melanoma patients.

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Background: Ipilimumab was the first agent approved for the treatment of unresectable or metastatic melanoma to show a survival benefit in randomised phase III trials. Efficacy and safety of ipilimumab treatment outside of clinical trials and the correlation with BRAF and NRAS mutation status were evaluated. **Methods:** Ipilimumab was available upon physician request for patients (pts) aged ≥16 years with unresectable stage III/stage IV melanoma who had either failed systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. BRAF and NRAS mutation status was retrospectively collected for all available pts. Patients were monitored for adverse events, including immune-related AEs, using Common Terminology Criteria for Adverse Events v.3.0. **Results:** In total, 855 Italian pts participated in the EAP from June 2010 to January 2012 across 55 centres. With a median follow-up of 6.5 months (range 0.5-30), the disease control rate among 833 pts evaluable for response was 34.3%: 28 pts (3.4%) with complete response, 83 (10.0%) with partial response and 175 (20.9%) with stable disease. As of December 2012, median progression-free survival and overall survival were 3.3 months and 7.2 months respectively, with 1-year survival rate of 36%. The Table shows mutation status for available patients. Disease control rates were comparable among pts with BRAF positive tumors and BRAF wild-type (37.5% vs 39.5%) and among pts with NRAS positive tumors and NRAS wild-type (57.1% vs 49.3%). Survival curves were also comparable between groups. 399 pts (46.7%) had a AEs of any grade, with 286 (33.5%) considered IrAEs. IrAEs were reversible with protocol specific guidelines. **Conclusions:** Based on EAP data, ipilimumab is an effective and safe treatment for pretreated pts with metastatic melanoma regardless BRAF and NRAS mutation status.

	Mutated	Wild-type	Total
BRAF	173 (36.9%)	296 (63.1%)	469
NRAS	14 (17.1%)	68 (82.9%)	82

9071 General Poster Session (Board #48B), Sat, 8:00 AM-11:45 AM

Upstream MAPK pathway inhibition: MEK inhibitor followed by a BRAF inhibitor in advanced melanoma patients.

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Background: The presence of activating BRAF mutations in about 60% of all metastatic melanomas (mM) has led to the development of inhibitors (i) targeting the RAF and MEK kinases. MEK is the downstream effector of BRAF. However, the blockage of the MAPK pathway is limited due to the development of resistance mechanisms. MEK resistance can confer cross-resistance to BRAF inhibition, whereas BRAF resistance is independent from the MAPK pathway. Hence, it seems reasonable to start a MAPK pathway inhibition by a BRAFi. An upstream inhibition beginning the treatment reversed with a MEKi followed by a BRAFi has not yet been clinically explored. **Methods:** Patients at the Dermatology Department of the University Hospital of Zurich with mM harboring a BRAF mutation formed the study cohort. Patients were divided into a group who was treated initially with a BRAFi (vemurafenib or LGX818) followed by a MEKi (AZD6244, trametinib, or MEK 162), and a group who first received a MEKi and was later treated with a BRAFi. Duration of disease control (DDC) was measured in time from the initiation of the treatment to discontinuation due to disease progression or toxicity. **Results:** A total of 16 patients (7 females, 9 males, age 30-73 years) with BRAF mutated mM were evaluated. The median DDC (mDDC) was similar in both groups. When patients were treated first with a BRAFi (n=7), the mDDC for BRAFi was 7.6 and for MEKi 1.7 months, respectively. In contrast, when the treatment sequence was inversed (n=9), the mDDC for MEKi was 3.9 and for BRAFi 4.7 months. We observed some benefit (partial response, stable disease) using chemotherapy after BRAFi/MEKi progression. **Conclusions:** This analysis indicates that the sequential MEK-RAF inhibition of the MAPK pathway is acceptable in BRAF mutant mM patients. The sum of the DDC of both groups (9.3 and 8.6 months) is comparable to the promising BRAFi/MEKi combination therapy (median PFS 9.4 months). Besides the sequenced administration analyzed here, an intermittent administration should be further studied.

9072 General Poster Session (Board #48C), Sat, 8:00 AM-11:45 AM

Thrombocytopenia associated with ipilimumab therapy of advanced melanoma at a single institution.

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Background: Ipilimumab (IPi) is a monoclonal IgG1κ antibody targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4) that was approved for the treatment of metastatic melanoma (MM). IPi therapy is associated with immune-related adverse events (irAEs) (Weber et al. *J Clin Oncol*2012 Jul 20;30(21):2691-7). Hematologic toxicity has rarely been reported. **Methods:** We analyzed 172 pts with MM treated adjuvantly or for metastatic disease with IPi on 2 clinical studies and an expanded access program (protocols MCC15283, MCC15722 and MCC15977). Clinical characteristics and hematologic parameters related to therapy were recorded. Medications, infections, comorbidities, prior therapies, and pathology reports from bone marrow (BM) biopsies were reviewed. **Results:** Of 172 subjects, 10 (5.8%) pts with normal platelet counts prior to therapy, developed thrombocytopenia (TCP) following IPi. Median number of doses was 8.5 (range 1-19). Median age at development of TCP was 64 years (range 21-93). Median time to development of TCP was 16.5 months (range 0.25 – 39). Of ten pts, three developed grade (gr) 1 or 2 TCP, three developed gr 3 and four pts developed gr 4 thrombocytopenia. BM analysis in pts with gr 4 TCP showed normal hematopoiesis and no evidence of melanoma. Six of 10 (60%) pts required therapy and were initiated on prednisone, but were deemed steroid refractory. No sustained responses to subsequent treatments with IVIG, rituximab, danazol, and/or splenectomy were observed. Three pts with grade 4 TCP were treated with eltrombopag. One of them achieved a sustained complete response lasting $>$ 20 months. The other 2 pts who received eltrombopag discontinued treatment due to vascular events. Three out of 10 (30%) pts with any gr of TCP experienced mild bleeding episodes in the form of epistaxis. One pt with gr 4 thrombocytopenia experienced severe gastrointestinal bleeding requiring hospitalization. No deaths related to bleeding occurred. **Conclusions:** This is the first case series of hematologic irAEs in pts treated with IPi on clinical trials, suggesting that steroid refractory TCP may occur with IPi treatment . The timing and severity of IPi associated TCP is highly variable so careful hematologic monitoring should be considered.

9073 General Poster Session (Board #48D), Sat, 8:00 AM-11:45 AM

Gender differences in survival from cutaneous melanoma: Analysis of United States SEER data, 1992 to 2009.

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Background: An accumulating body of evidence suggests that the outcome of early-stage melanoma is influenced by endocrine and menopausal status. However, it remains controversial as to whether the superior female melanoma-specific survival (MSS) is restricted to early stage disease or if it also pertains to patients with metastatic melanoma (MM). **Methods:** We analyzed data from the 13 registries that participate in the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program. We identified all cases of primary invasive melanoma diagnosed between 1992 and 2009; none of the patients had a prior history of another cancer. MSS was compared between males and females, stratified by stage of disease. Age groups were defined as 18-45y, 46-54y, 55-64y, 65+y as a proxy of female menopausal status. **Results:** The study population included 87,165primary invasive melanoma cases (unstaged n=2834). MSS was significantly poorer for males compared to females for localized (n=72,456) and regional (n=8,945) disease for all age groups (Hazard ratio (HR) ranging from 1.21 to 2.09, all $p<0.001$). MSS was not significantly different between males and females for patients with distant disease at diagnosis (n= 2930; HR 0.99, 0.92, 1.11, 1.07 for each age group) and remained non-significant after adjusting for Breslow thickness, histologic subtype, anatomic site, and age group (adjusted HR 1.04 males vs. females; 95% CI 0.95-1.14; p=0.41). **Conclusions:** While our results were consistent with earlier reports that women have higher MSS rates compared to men for early (stage I-III) melanoma, the intriguing finding of this study was that the female survival advantage does not vary with age or menopausal status as compared to men, which is contrary to previously published reports. Furthermore, we found that the difference in survival was no longer significant for patients with MM, suggesting that sex may influence local and regional, but not distant cancer progression.

9074 **General Poster Session (Board #48E), Sat, 8:00 AM-11:45 AM**

Relevance of MIA and S-100 to monitor BRAF inhibitor (iBRAF) therapy in metastatic melanoma patients.

Miguel F. Sanmamed, Sara Fernandez-Landazuri, Eduardo Castanon, Jose Echeveste, Maria D. Lozano, Miguel A. Idoate, Jose Luis Perez-Gracia, Alvaro Gonzalez, Salvador Martin-Algarra; Department of Oncology, University of Navarra, Pamplona, Spain; Department of Biochemistry. University of Navarra, Pamplona, Spain; Department of Oncology. University of Navarra, Pamplona, Spain; Department of Pathology. University of Navarra, Pamplona, Spain

Background: MIA and S-100 have been proposed as tumor markers for patients with melanoma, but they are not widely accepted. BRAF V600E mutation has been reported in more than 50% of melanomas. Recently, selective BRAF inhibitors have proved to be more active than DTIC in first line treatment of BRAF V600E melanoma patients. The aim of the present work is to evaluate the utility of MIA and S-100 during iBRAF treatment. **Methods:** BRAF V600E mutation was analyzed in 77 patients with metastatic melanoma by automated direct sequencing in tumor DNA. Tumor markers (MIA, S-100 and LDH) were studied in serum from all patients. Sixteen of these patients received iBRAF therapy (11 Vemurafenib, 5 Dabrafenib) and tumor markers were analyzed sequentially: baseline, best response and progression. MIA and S-100 were determined by immunometric methods and LDH by a spectrophotometric assay. The cut-off points were MIA=9 ug/L, S-100=0.1 ug/L, and LDH=290 U/L. Non-parametric statistical analysis was performed. **Results:** Forty-three patients had BRAF V600E mutation and 34 were wild type (WT). The percentage of cases with MIA above the cut-off in patients with V600E mutation was significantly higher than in the WT group (76.3% vs. 52.9%; $p<0.05$), while the frequency of elevated S-100 and LDH was similar. Among patients treated with iBRAF, the response rate was 87.5% (5 CR, 9PR). In responding patients, MIA and S100 levels decreased dramatically, but not LDH (Table). At the time of this report, thirteen patients have progressed. Upon progression, MIA and S-100 increased significantly above levels achieved at best response (Table). **Conclusions:** Serum MIA and S-100 are potentially useful markers in the clinical and follow-up management of patients receiving iBRAF therapy. Validation in a larger series is needed.

MIA, S-100 and LDH values at baseline, best response, and progression.

	Baseline M (Q1-Q3)	Best response M (Q1-Q3)	B vs BR p	Progression M (Q1-Q3)	BR vs P p
MIA (μg/L)	17 (13-44)	9.4 (7.6-11.3)	<0.01	13 (10.3-17)	<0.01
S-100 (μg/L)	0.43 (0.13-6)	0.07 (0.06-0.15)	<0.01	0.2 (0.05-1.1)	<0.05
LDH (U/L)	258 (221-768)	213 (183-235)	NS	213 (192-529)	NS

M: Median. NS: no significant.

9075 General Poster Session (Board #48F), Sat, 8:00 AM-11:45 AM

High-dose interleukin-2 (HD IL-2) in the treatment of advanced melanoma: The University of Pittsburgh experience.

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Background: IL-2 is a T-cell growth factor tested in a variety of regimens for advanced melanoma (MEL) and renal cell carcinoma (RCC). High-dose IL-2 (600,000-720,000 IU/kg administered intravenously every 8 hours for up to 14 consecutive doses) was approved by FDA for advanced MEL and RCC in 1998 based upon the durability of responses observed. Early studies of HD IL-2 reported overall (OR) and complete response (CR) rates of 16% and 8% respectively. Severe toxicity limited use to specialized centers with standardized protocols, either intensive care (ICU) or oncology specialty settings. The U Pittsburgh has treated 1022 patients with IL-2 at any dosage and we here present outcomes of 550 MEL pts treated with HD IL-2 in an oncology specialty non-ICU setting. **Methods:** Clinical and radiological data were collected on all pts treated with IL-2 using the UPCI Cancer Registry and Medical Archival System (MARS). Pharmacy records were reviewed for dosing details. The influence of baseline characteristics on treatment outcomes was assessed using Cox proportional hazards analysis. **Results:** A total of 848 pts received HD IL-2, of which 298 pts had RCC while 550 had MEL. Detailed pharmacy dosing records were reviewed from 176 pts treated over the past 12 years (2000-2012) who received a total of 3738 cycles. Of 165 pts evaluable for response, OR was documented in 24 pts (14.8%) and CR in 5 pts (3.0%). Median overall survival (OS) was 10.0 mos for all patients and 21.5 mos for responders (CR+PR). Median number of doses per cycle was 7. Toxicity was consistent with prior reports. HD IL-2 required ICU transfers in 5% and 1 death was attributed to HD IL-2. Pts with higher baseline lactate dehydrogenase (LDH) had poorer OS ($p < 0.05$). **Conclusions:** In this large and uniformly treated series of recent patients treated with IL-2 OR/CR rates with HD IL-2 are 14.8% and 3.0% respectively. Higher LDH is associated with poorer outcome. Biomarkers of response are currently being evaluated in banked clinical specimens collected from patients under the SPORE in Skin Cancer (P50 CA121973).

9076 General Poster Session (Board #48G), Sat, 8:00 AM-11:45 AM

A phase I study of the combination of sorafenib (Sor) and bortezomib (Bor) in patients (pts) with metastatic melanoma (MM).

Ryan J. Sullivan, Nageatte Ibrahim, Donald P. Lawrence, Julie Aldridge, F. Stephen Hodi, Keith Flaherty, Christine Conley, Sarah DeNoble, James Walter Mier, Daniel C. Cho, Michael B. Atkins, David F. McDermott; Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; International Beast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC

Background: Sor is a small molecule tyrosine kinase inhibitor that has many targets and previously was developed for the treatment of MM. Bor is a proteasome inhibitor widely used to treat multiple myeloma and other malignancies. In preclinical studies, the combination of Sor and Bor has been shown to modulate expression of BCL-family members and augment cytotoxicity in MM cell lines. **Methods:** Pts with MM were enrolled in cohorts of 3 during dose escalation to determine the maximum tolerated dose (MTD) of Sor twice daily (BID) in combination with Bor given days 1, 8, 15 of a 28 day cycle. The MTD was defined as the highest dose level at which less than 33% of pts exhibited a dose limiting toxicity (DLT). Efficacy, as measured by 6-month progression free survival (PFS) and response rate (RR) per RECIST, was documented. **Results:** Eleven pts were enrolled in 3 dose levels. DLTs (fatigue and rash respectively) were seen in 2 of 3 patients enrolled at the highest dose level (Sor 400 mg and Bor 1.3 mg/m^2). The next lowest dose level (Sor 400 BID and Bor 1.0) enrolled 5 pts and none had DLTs. Thus, this dose level was defined as the MTD. Toxicities seen in $>$20% of pts included hypertension, pruritus, hand-foot syndrome, mucositis, nausea, vomiting, rash, constipation, abdominal pain, anorexia and fatigue. Of 9 response evaluable pts, none had radiographic evidence of tumor response. Two of 11 (18%) pts remained progression free for greater than 6 months. **Conclusions:** The combination of Sor and Bor is safe, but minimally active in pts with MM. In the absence of tumor response at or above the MTD, the study was closed with only 5 pts treated at the provisional MTD and enrollment to a planned dose expansion cohort will not occur. Clinical trial information: NCT01078961.

9077 **General Poster Session (Board #48H), Sat, 8:00 AM-11:45 AM**

Trends and variations in the use of adjuvant immunotherapy for stage III melanoma in the U.S. population.

Teresa J. Nasabzadeh, Huei-Ting Tsai, Eshetu Tefera, Suraj S. Venna, Arnold L. Potosky, Michael B. Atkins, Sekwon Jang; Medstar Washington Hospital Center, Washington, DC; Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; MedStar Health Research Institute, Hyattsville, MD; Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC

Background: High dose Interferon alfa-2b (IFN), an adjuvant immunotherapy for patients (pts) with stage III melanoma, was the only approved treatment option in the US from 1995-2011. There is limited information on how high dose IFN has been disseminated to eligible pts in general clinical practice, and whether variations exist in its adoption according to non-clinical factors. **Methods:** We obtained data on 34,208 pts diagnosed between 1998-2010 with stage III melanoma from the National Cancer Data Base (NCDB). IFN treatment was abstracted as immunotherapy. We investigated the use of immunotherapy according to pt demographic, socioeconomic, and clinical variables. We conducted multiple logistic regression analysis to examine the effect of these variables on the receipt of immunotherapy. **Results:** 62% of pts in our study population were male, 88% were Caucasian and 31% were over age 65. Overall, 27% of the pts received immunotherapy. There was no significant trend in its adoption between year 1998 and 2010. After adjustment for clinical variables, age at diagnosis, facility type, and geographic region are predictors strongly associated with use of immunotherapy. Only 16% of pts aged 65-74 and 3% over 75 received immunotherapy compared to 42% of those ages less than 45 (adjusted ORs 0.44 [0.32-0.59], 0.05 [0.04-0.14), respectively). Also 24% of pts treated at a comprehensive community cancer program received immunotherapy compared to 30% of those treated at an academic/research program (OR, 0.71 [0.51-0.99]). The frequency of immunotherapy was 25% in the Atlantic region and 17% in the Western region compared to 33% in Northeast (ORs 0.42 [0.18-0.99], 0.31 [0.13-0.74], respectively). Median household income, insurance type and comorbidity were not associated with adoption of immunotherapy after adjustment for all other variables. **Conclusions:** Less than one-third of all eligible patients received adjuvant immunotherapy in US general practice over the past decade. There is significant variation in its adoption according to non-clinical factors. Further exploration of the reasons for these variations and whether they are linked to important patient outcomes is needed.

9078 General Poster Session (Board #49A), Sat, 8:00 AM-11:45 AM

Dissection of anti-CTLA4-induced cytotoxic T-cell responses in melanoma.

John B. A. G. Haanen, Pia Kvistborg, Daisy Philips, Sander Kelderman, Bianca Heemskerk, Christian Ottensmeier, Daniel E Speiser, Olivier Alain Michielin, Emanuela Romano, Christian U. Blank, Ton Schumacher; The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; The Netherland Cancer Institute, Amsterdam, Netherlands; The Netherlands Cancer Institute-Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; Southampton University Hospitals NHS Foundation Trust, Southampton, United Kingdom; Ludwig Institute for Cancer Research, Lausanne, Switzerland; University Hospital Lausanne, Lausanne, Switzerland

Background: There is strong evidence that melanoma-reactive T cells induced by immunotherapeutic interventions such as anti-CTLA4 therapy can exert clinically effects. However, there is very little information on how these therapies influence tumor-specific T cell responses. Furthermore, as the number of potential melanoma-associated antigens to which these responses can be directed is very high, classical strategies to map cytotoxic T cell reactivity do not suffice. Knowledge of such reactivities would be useful to design targeted strategies, selectively aiming to induce immune reactivity against these antigens. **Methods:** We have addressed these issues by designing MHC class I molecules occupied with UV-sensitive 'conditional' ligands, thereby allowing the production of very large collections of pMHC complexes for T cell detection. Secondly, we have developed a 'combinatorial coding' strategy that allows parallel detection of dozens of different T cell populations within a single sample. The combined use of MHC ligand exchange and combinatorial coding allows the high-throughput dissection of disease- and therapy-induced CTL immunity. We have used this platform to monitor immune reactivity against a panel of 145 melanoma-associated epitopes in patients receiving Ipilimumab treatment. **Results:** Comparison of PBMC samples from 32 melanoma patients pre- and post-therapy indicated a significant increase in the number of detectable melanoma-associated T cell responses ($p=0.004$). Furthermore, kinetic data on T cell responses during therapy suggests that this broadening generally occurs within weeks after start of therapy. The magnitude of melanoma-specific T cell responses that was detectable prior to start of therapy was not significantly altered ($p=0.8$). **Conclusions:** These results establish the pattern of melanoma-specific T-cell reactivity induced by anti-CTLA4 treatment and form a benchmark for evaluation of other immunotherapeutic interventions, like anti-PD1 treatment, that are currently undergoing clinical evaluation. Furthermore, our data suggests that the clinical activity of Ipilimumab may be mostly due to epitope spreading, rather than through enhancement of pre-existing immune activity.

9079 General Poster Session (Board #49B), Sat, 8:00 AM-11:45 AM

A phase IB study of ipilimumab with peginterferon alfa-2b in patients with unresectable melanoma.

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Background: Peginterferon alfa-2b (Sylatron) as adjuvant therapy has been shown to benefit patients with high-risk resected melanoma and some interferon studies have shown that the induction of autoantibodies may correlate with benefit. Ipilimumab (IPI, Yervoy) is a fully human anti-CTLA-4 antibody that induces autoimmune toxicity that in some cases appears to correlate with clinical benefit. This study was performed to assess whether ipilimumab can be safely administered with peginterferon alfa-2b. **Methods:** This study combined IPI at 3mg/kg every 3 weeks for 4 doses along with concurrent peginterferon alfa-2b at 3 mcg/kg weekly for up to 156 weeks or until disease progression, unacceptable toxicity or patient decision to discontinue. The study was designed to obtain toxicity, tolerability and autoimmune antibody data and to define a well-tolerated dose of the combination. **Results:** Median age was 61 with 9 female and 8 male subjects. There were 3 patients (pts) with partial responses, 1 stable disease, and 6 with progressive disease in 10 pts evaluable for response thus far. Six pts have not yet completed cycle 1 and therefore are not evaluable for response at the time of this publication but will be presented. One pt withdrew consent prior to finishing cycle 1. Toxicities from peginterferon alfa-2b 3mcg/kg were dose-limiting with 7 pts requiring dose reduction in peginterferon alfa-2b secondary to toxicity. The Grade 3 events leading to dose reductions were nausea and vomiting, leucopenia, dehydration, and hyponatremia. peginterferon alfa-2b was dose reduced to 2 mcg/kg weekly in future pts after these toxicities were noted. No Grade 3 or 4 toxicities attributable to ipilimumab have occurred thus far. No Grade 3 or 4 events have been noted to date in the10 pts initiated at 2 mcg/kg of peginterferon alfa-2b. There was no significant change in the presence autoantibodies (ANA, anti-double stranded DNA, antithyroglobulin, antimicrosomal antibodies, and anticardiolipin antibodies) between responders and non-responders in the evaluable pts. **Conclusions:** Peginterferon alfa-2b added to IPI results in an excellent response rate in this small population. Peginterferon alpha-2b at 2 mcg/kg weekly with IPI at 3 mg/kg every 3 weeks appears well-tolerated and the combination warrants further exploration. Clinical trial information: NCT01496807.

9080 General Poster Session (Board #49C), Sat, 8:00 AM-11:45 AM

Blood mRNA signature to predict survival in patients with metastatic melanoma treated with tremelimumab.

Yvonne M. Saenger, Jay Magidson, Bobby Chi-Hung Liaw, Karl Wassmann, William Barker, Sara Harcharik, David Fisher, William K. Oh, Philip Friedlander; Mount Sinai School of Medicine, New York, NY; Statistical Innovations, Inc., Belmont, MA; Mount Sinai Medical Center, New York, NY; GeneNews, Boston, MA; Massachusetts General Hospital, Boston, MA; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Tremelimumab (Ticilimumumab, Pfizer), a monoclonal antibody targeting CTLA-4, a T cell inhibitory molecule, has shown activity in metastatic melanoma. Ipilimumab (Yervoy, BMS), another antibody targettingCTLA-4, improves survival relative to a peptide vaccine and is now FDA approved. A minority of patients will achieve durable tumor control with CTLA-4 blockade and biomarkers are urgently needed to identify those patients. **Methods:** 170 inflammatory, melanoma-specific and CTLA4-pathway related mRNA transcripts were measured using RT-PCR in pre-treatment peripheral blood samples from 218 patients with refractory melanoma receiving tremelimumab in a multi-center phase II study. A 2-class latent model yielded a risk score based on 4-genes that was highly predictive of survival ($p<0.001$), and was used to categorize patients into low, medium and high-risk groups. An independent cohort of 260 treatment naïve melanoma patients receiving tremelimumab as part of a multi-center phase III study was then used to validate the risk score as well as the 3 risk groups defined using the pre-specified cut-points. **Results:** There was no significant difference between the two cohorts in terms of age, gender, stage of disease or ECOG status. Median time of follow up was 297 days for the training cohort and 386 days for the validation cohort. 67% of patients in the training cohort and 70% of patients in the validation died during time of follow-up. Collectively, the ability of the 170 genes to predict survival exhibited a high degree of consistency across the cohorts ($p < 0.001$). A 4-gene model including cathepsin D (CTSD), Phopholipase A2 group VII (PLA2G7), Thioredoxin reductase 1 (TXNRD-1) and Interleukin 1 receptor associated kinase 3 (IRAK3) predicted survival in the validation cohort ($p=0.001$ by log rank test). Multivariable cox analysis showed that the 4-gene model added to the predictive value of clinical predictors ($p<0.0001$). **Conclusions:** Expression levels of CTSD, PLA2G7, TXNRD1, and IRAK3 in peripheral blood are predictive of survival in melanoma patients treated with ticilimumab (αCTLA-4). Blood mRNA signatures should be further explored to define patient subsets likely to benefit from immunotherapy.

9081 General Poster Session (Board #49D), Sat, 8:00 AM-11:45 AM

Response rate to vemurafenib in BRAF-positive melanoma brain metastases.

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Background: Brain is a common site for melanoma metastases. Responses to dabrafenib have already been reported in over 50% of patients. We aimed at assessing response rate (RR) to vemurafenib (Vem). **Methods:** Patients with BRAF positive melanoma and asymptomatic brain metastases at initiation of Vem were eligible. Records were analysed retrospectively to calculate RR (at least 30% decrease in the sum of diameters of target lesions), duration of response and time to CNS progression (TTP). **Results:** 18 patients with CNS metastasis received Vem (M/F=8/10; median age 50); 9 received no prior therapy to the brain (group A), 6 had previous surgery and/or radiotherapy with residual disease (group B; n=6), 3 patients had prior ″brain therapy″ but with evidence of progression in CNS before the start of Vem and were added to group A (n=9+3=12). 50% RR was observed in group A; 5 had no prior therapy, 1 relapsed after resection/WBRT. Duration of response was: 8, 8, 8, 16, 32 weeks and 1 not reached yet. Similarly, 50% RR was observed in group B; however contribution of Vem to CNS control in this group was more difficult to assess. Duration of responses: 4, 26, 33 weeks. All except 2 patients progressed in CNS before, or at the time of, systemic progression. Median TTP in group A was: 21 weeks (16-41) in responding patients and 12 weeks (4-22) in those without a response (includes SD). Median TTP in group B = 44 weeks (16-60) in responders, 8 weeks (3-16) in non-responders. **Conclusions:** Vemurafenib resulted in 50% CNS response rate. Prospective comparison to dabrafenib may be warranted.

9082 General Poster Session (Board #50A), Sat, 8:00 AM-11:45 AM

Updated interim analysis of UCI 09-53: A phase II, single arm study of pazopanib and paclitaxel as first-line treatment for subjects with unresectable advanced melanoma.

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Background: Metastatic melanoma lacks effective therapy. Pazopanib is an inhibitor of VEGFR-1,2,3, PDGFR-B and c-KIT that has antiangiogenic activity in renal cell cancer as well as inhibition of melanoma tumor xenografts. We designed a phase II single arm, open label clinical trial evaluating pazopanib in combination with metronomic paclitaxel as first line therapy for subjects with unresectable stage III and stage IV melanoma. **Methods:** This protocol utilizes a Simon 2-stage Minimax design, with a planned interim analysis to confirm >3 responders to move to the second stage. To date, 31 patients are evaluable for response. All subjects were treatment naïve and received paclitaxel at 80mg/m2 weekly for three weeks in a 4 week cycle and pazopanib 800mg continuous daily oral dose. The primary endpoint is 6 month progression free survival. Exploratory endpoints include biomarker analysis that may be associated with treatment outcomes (serum VEGF, soluble VEGFR-2, serum HIF, serum TSP1 and BRAF mutation status). An additional exploratory endpoint includes the in vitro activity of pazopanib and paclitaxel on patient biopsy material co-cultured with vascular endothelial cells. RECIST 1.1 criteria were used to define treatment response (SD criteria was a minimum interval of 8 weeks). **Results:** For the 31 evaluable patients treated to date the following results were seen: 1 CR, 9 PR's, 13 SD's and 8 PD's. The overall RR (CR+PR) was 32%. Total disease control rate was 74% (CR+PR+SD). The most common AEs/lab abnormalities were diarrhea (66%) nausea (60%), hypertension (63%), fatigue (63%) and vomiting (29%). Grade 3-4 AEs included hypertension (26%), transaminitis (23%) and neutropenia (17%).One patient discontinued for grade 4 transaminitis which subsequently resolved completely. Dose reductions were required for pazopanib in 15 patients and for paclitaxel in 4 patients. **Conclusions:** Updated interim analysis of this phase II study demonstrated that pazopanib in combination with paclitaxel was well tolerated and resulted in a 32% response rate, indicating that this combination is of further interest. Accrual will continue to reach a goal of 60 patients. Clinical trial information: NCT01107665.

9083 **General Poster Session (Board #50B), Sat, 8:00 AM-11:45 AM**

Treatment patterns in patients with early and advanced malignant melanoma.

Victor M. Gastanaga, Jan E. Lethen, Ari M. Vanderwalde, Lori A. Cyprien, Michael A. Kelsh, Joel D. Kallich; Amgen, Inc., Thousand Oaks, CA

Background: We seek to characterize tx patterns for patients (pts) with early stage (ES) and advanced stage (AS) malignant melanoma (MM). MarketScan is a large insurance claims database with complete diagnosis (dx) and tx information. **Methods:** Using MarketScan data, pts were identified between Jan 2001 and Jun 2011 using ≥1 inpatient or ≥2 outpatient MM ICD9 codes ≥6 weeks apart. Pts with a history of other malignancies or lacking records at least 1 year prior to diagnosis were excluded. Pts were considered AS if they received chemotherapy, interferon, ≥2 days of MM surgery, or a code of secondary metastases. All other pts were classified as ES. Radiotherapy, immunotherapy, chemotherapy, and surgery type were identified with HCPCS, CPT, and ICD9 procedure codes. Pts were categorized by type of progression (ToP): AS at time of dx (AS-D), ES at dx with progression to AS during follow-up (ES-P), and ES at dx with no progression during follow up (ES-NP). **Results:** Of 30,678 eligible pts, 55% were male, median age was 59 yrs, and median follow-up was 31 months. Initial disease locations were head and neck (21%), torso (27%), upper extremities (17%), and lower extremities (14%). Twenty-five percent (7607 pts) were identified as having AS MM during follow-up. Of these, 2,445 (8%) were AS-D, while 5162 (17%) were ES-P. The remaining 23,071 pts (75%) were ES-NP. Frequency of most extensive surgery type after diagnosis date are shown by ToP (table). No ES-NP pts received systemic tx during follow-up, but 21% of ES-P and 64% of AS-D pts received either chemotherapy, immunotherapy, or both. Agents most commonly prescribed in AS pts were interferon and temozolomide. **Conclusions:** The tx burden in MM pts is extensive and appears to increase with disease severity. Claims data can be a valuable tool in elucidating MM tx patterns by disease stage.

Extent of surgery by disease type (%).

	ES-NP	ES-P	AS-D
None	37	9	30
Biopsy	5	1	2
Wide local excision	37	58	8
Sentinel node biopsy	18	25	21
Lymph node dissection	3	7	39

9084 General Poster Session (Board #50C), Sat, 8:00 AM-11:45 AM

Changes in the quality of life of advanced melanoma patients after 12 weeks of treatment with ipilimumab compared to gp100 in a phase III clinical trial.

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Background: This study analyses health-related quality of life (HRQL) outcomes for ipilimumab (ipi) with and without gp100 and gp100 alone during the 12 week treatment (T) induction period compared to baseline. The aim of this study was to express the HRQL as proportions of patients experiencing changes during the induction period, when most of the immune-related adverse events (ir-AE) on ipi occur. **Methods:** Data from the MDX010-20 trial, including 676 previously treated patients (pts) with unresectable stage III or IV melanoma, was analysed. Differences between ipi with/without gp100 and gp100 alone in terms of HRQL 12 weeks after randomisation according to the EORTC QLQ-C30 were searched for. The sample consisted of 388 pts (ipi: 83; ipi + gp100: 227; gp100: 78) completing both baseline and week (W)12 questionnaires. Ordinal regression was performed for these pts to determine a T effect on W12 scores (in ordered categories) whilst adjusting for key covariates. Fisher's Exact Test was used to detect differences between Ts for each EORTC domain when considering mean change in scores, categorised as "clinically worse" ($\leq$-10 on functional domains, $\geq$10 on symptoms), "stable" ($>$-10 to $<$10) and "clinically improved" ($\geq$10 on functional domains, $\leq$-10 on symptoms). **Results:** There were no significant differences for any domain score between the 3 T arms at W12. The odds of attaining high HRQL scores at W12 were heavily dependent on the baseline scores; baseline scores explained most of the variability as per regression analysis. There was no significant difference between the 3 T arms in terms of pts showing a clinically significant reduction or improvement in HRQL. HRQL remained globally stable from baseline to W12, in $>$ 50% of pts for most domains. **Conclusions:** Ipi with/without gp100 does not have a significant negative HRQL impact in stage III-IV melanoma during the T induction phase relative to gp100 alone after adjustment for differences in baseline scores. The lower rate of pts showing HQRL reduction and the absence of difference with gp100 suggest that ir-AE have little impact on HRQL. Further HRQL studies are needed, as efficacy benefits of ipi continue after W12.

9085 General Poster Session (Board #50D), Sat, 8:00 AM-11:45 AM

Use of tumor exome analysis to reveal neo-antigen-specific T-cell reactivity in ipilimumab-responsive melanoma.

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Background: Evidence for T cell mediated regression of human cancer in particular melanoma following immunotherapy is strong. Anti-CTLA4 treatment has been approved for treatment of metastatic melanoma and blockade of PD-1 has shown encouraging results. However, it is unknown which T cell reactivities are involved in cancer regression. Reactivity against non-mutated tumor self-antigens has been analyzed in patients treated with Ipilimumab or with autologous TILs, but the size of these responses are modest. Therefore, T cell recognition of patient-specific mutant epitopes may be a potentially important component. Animal model data recently suggested that analysis of T cell reactivity against patient-specific neo-antigens may be feasible through exploitation of cancer genome data. However, human data have thus far been lacking. **Methods:** To address this we have used MHC class I peptide exchange technology allowing production of very large collections of pMHC complexes, together with a pMHC ″combinatorial coding″ strategy for parallel detection of dozens of different T cell populations within a single sample. **Results:** From a melanoma patient responding to ipilimumab treatment, we identified tumor specific mutations via exome sequencing of tumor material. The exome contained 1,075 non-synonymous mutations. Possible MHC epitopes covering these mutations were predicted based on; 1) predicted to bind the patient's MHC; 2) predicted to be cleaved by the proteasome; 3) genes of which the mutated peptides arose had evidence of RNA expression. The analysis yielded 1,952 epitopes restricted to the HLA-A and HLA-B. To screen for T cell reactivity against these epitopes we used the pMHC combinatorial coding approach. We found T cell reactivity against 2 neo-antigens, including a dominant T cell response against a mutant epitope of the ATR gene product. Analysis of PBMC samples collected before and during Ipilimumab therapy showed that this particular response increased strongly after treatment from 0.06% to 0.28% of CD8 T cells after being stable in magnitude for 10 months. **Conclusions:** These data provide the first demonstration of cancer exome-guided analysis to dissect the effects of melanoma immunotherapy.

9086 General Poster Session (Board #51A), Sat, 8:00 AM-11:45 AM

Graded prognostic assessment index for melanoma with brain metastases (MBM).

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Background: The Graded Prognostic Assessment (GPA) is a commonly used prognostic index in patients with brain metastases (BM). GPA for melanoma consists of Karnofsky Performance Scale (KPS) and the number of BM present. The purpose of this study was to evaluate the utility of GPA index in a contemporary cohort of patients (pts) with MBM at a single institution to predict Overall Survival (OS). **Methods:** With IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center's database was used to identify pts with MBM treated between 2000-2012. The primary endpoint was OS from diagnosis of MBM. Cox proportional hazards models were used for data analysis. Stepwise variable selection was used to identify independent prognostic factors. **Results:** 90 MBM (51 females) median age 57 years (range 24-87) were included for analysis. The median number of BM was 2 (range, 1-11). KPS was 90-100(52%), 70-80 (43%) and <70 (6%). Extracranial metastases was present in 75 patients (83%). Initial treatment included Stereotactic Radiosurgery (SRS) (49%), Whole Brain Radiotherapy (WBRT) (8%), WBRT + SRS (22%), WBRT + Surgery (S)(14%) and SRS + (S) (7%). Median OS was 7.8 months (95% C.I. 6.8-10.1). GPA was prognostic for OS (p=0.01), however this was because pts with scores of 4 had worse outcomes (median 5.1months) than the other 3 groups, which had similar OS (median 9.0-12.8 months). In addition, number of BM was not associated with OS (p=0.19). In contrast, KPS (p=0.02), Liver (p=0.04) and hemorrhagic metastasis (p=0.02) were independently prognostic for OS. These factors can be used to derive a new prognostic index with 3 groups: Unfavorable, Intermediate and Favorable (see Table). **Conclusions:** GPA was prognostic for OS in pts with MBM, however separation of the groups was not clear. A new prognostic index consisting of KPS, liver and hemorrhagic metastases is proposed for MBM.

New prognostic index.

Prognostic group	No. of points	N	Median survival (months)	P
Unfavorable	0-1	18 (22%)	4.4	
Intermediate	2	38 (46%)	8.4	
Favorable	3	27 (33%)	12.8	<0.0001

9087 **General Poster Session (Board #51B), Sat, 8:00 AM-11:45 AM**

A phase I study of high-dose calcitriol in combination with temozolomide for patients (Pts) with metastatic melanoma (MM).

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Background: Temozolomide (Tem) has demonstrated efficacy as an oral alternative for pts with MM on traditional and extended dosing schedules. Calcitriol has known antiproliferative properties in vitro, and has shown synergistic effects with chemotherapy. Additionally, vitamin D receptor (VDR) polymorphisms are associated with alterations in melanoma susceptibility and disease progression. Specifically, the VDR genotype tt/ff (Taq1 and Fok1 polymorphisms) has been associated with tumors >3.5mm, though no studies have focused on survival. **Methods:** Tem 150mg/m^{2}was administered on days 2-8 and 16-22 every 28 days until progression or significant toxicity. Calcitriol was given on days 1 and 15 every 28 days with 3 pts at a dose of 0.2mcg/kg, 3 pts at 0.3mcg/kg, 3 pts at 0.5mcg/kg, and an additional 11 pts at a maximum dose of 0.5mcg/kg. VDR gene analysis was completed on 17/20 pts using PCR-RFLP based assays. Tolerability was the primary objective with secondary objectives of time to progression (PFS) and overall survival (OS), both as a whole and by VDR genotype. **Results:** Twenty pts (males=15) with MM treated with at least one prior systemic therapy or who were not candidates for interleukin-2 (conducted pre BRAF and anti CTLA agents), were accrued. Median age was 58. The regimen was well-tolerated with leukopenia, lymphopenia, thrombocytopenia, anemia, and thrombosis as the most common grade 3 or 4 toxicities at 10% incidence each, less than observed in prior studies (Patel et al Eur J Ca 2011). Obj RR was 10%. Median PFS was 1.8 mo with a mean of 2.7 cycles given. Pts with low-risk VDR genotype non-tt or ff (n= 11) had a median OS of 7.4 mo compared to 3.8 mo for tt or ff or both (n=6)(median ratio=1.95) from time of enrollment, although not statistically significant given small sample sizes. **Conclusions:** The extended dosing of Tem with calcitriol is a well-tolerated oral regimen in MM. The trend toward improved OS in non-tt/ff VDR genotypes is consistent with prior studies associating the tt/ff genotype with biologic aggressiveness. Whether this represents a benefit of the inclusion of calcitriol should be studied further. Clinical trial information: NCT00301067.

9088 General Poster Session (Board #51C), Sat, 8:00 AM-11:45 AM

Gamma knife stereotactic radio-surgery and BRAF inhibition in metastatic melanoma.

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Background: Gamma knife radio-surgery (GK) is an effective approach to treating brain metastases in patients with metastatic melanoma. BRAF inhibition with vemurafenib produces a median progression free survival (PFS) of 7 months, but low central spinal fluid penetration may limit its effectiveness in patients who develop brain metastases. We report long term follow-up of patients with BRAF mutant melanoma treated with vemurafenib and GK. **Methods:** Demographics and clinical outcomes were characterized for 18 BRAF mutant melanoma patients with brain metastases treated between 2007 and 2012 with GK and with vemurafenib (vem) for >1 month. **Results:** The median age at starting vem was 51 yrs (range 34-76). 61% of the patients were women. Patients were treated with a median of 1 prior therapy (range 0-3). 7/18 patients (39%) had brain involvement prior to starting vem. 16/18 patients (89%) had stage M1c disease at the time of starting vem. Patients were treated with vem for a median of 8.4 months (range 2.1 to 27 months), had a median survival of 15.7 months after starting vem (range 4.2-29.4), and a median survival after GK of 7.8 months (range 1.2-21.1). Patients underwent GK to a median of 3 lesions (range 1-6). In total, 8/18 patients (44%) were treated with WBRT. 7/18 patients underwent craniotomies, 2 of which were for progression in lesions treated with GK, and 4 of which were also among the patients treated with WBRT. In 7/18 patients treated with GK for new brain progression after starting vem, vem was continued after GK for a median duration of 4.1 months (range 1.3 to 15.8). In these 7 patients that had vem and GK and continued vem, the median overall survival after starting vem was 19.9 months (range 6.7 to 29.3). Of these 7 patients, 4 required whole brain radiation therapy (WBRT); 3 have not required any additional brain directed therapy, including 2 patients who continue on vemurafenib at the time of analysis. 5/18 patients were treated with more than 1 round of GK, 3 of which were subsequently treated with WBRT. **Conclusions:** Despite the brain being a common site of progression on vemurafenib therapy, long term survival can be achieved in some cases by continuing vem after GK therapy.

9089 **General Poster Session (Board #51D), Sat, 8:00 AM-11:45 AM**

Melanoma recurrence risk stratification using Bayesian systems biology modeling.

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Background: Estimating the risk of recurrence in patients with melanoma is extremely challenging. Standard of care is AJCC staging system, but the accuracy and robustness of this method is still under development. We conducted a proof of concept study exploring the use of machine-learned Bayesian Belief Networks (ml-BBNs) using a miRNA profiled cohort of melanoma patients with extended follow up to create Bayesian Biological Systems Models (BBSMs). We sought to determine if ml-BBNs could describe the biological system and if we could use the model to identify new cases with higher risk of recurrence. **Methods:** Our study cohort consisted of 89 patients (42 of which recurred) with a median follow up time of 118 months, that were examined for 869 miRNAs. Prior to modeling we segmented the data into training data (72 cases/80%) and testing data (17 cases/20%) at random. We recursively trained ml-BBNs on the training set, using all miRNAs. We used the directed graph structure of the ml-BBNs to identify miRNAs that consistently had more connectivity and goodness of fit as determined by Bayesian Information Criteria (BIC) scoring. MiRNAs that were in the top 50 BIC-scoring nodes across all models were selected for use to train the recurrence BBSMs. To compensate for a small number, bootstrapping was used to increase the sample to 100 records. We then compared our test set cases to our recurrence model, and used a similarity scoring algorithm to evaluate the similarity of values in each test instance to our biological models. For comparison we also trained an ml-BBN using clinical data from the same cohort. We then evaluated the scores against known recurrence outcome using Receiver Operating Characteristic (ROC) curve analysis. **Results:** BIC-scoring analysis selected 35 miRNAs for use in BBSM modeling. Area Under the Curve (AUC) for detection of recurrence is 0.76 in the training set and 0.62 in the testing set, while the clinical data yielded an AUC of 0.5 in this cohort. **Conclusions:** Our data suggest that ml-BBNs can be used to describe a biological model of melanoma recurrence. Additional data and refinement need to be made using independent datasets to be of a level that is clinically useful.

9090 General Poster Session (Board #51E), Sat, 8:00 AM-11:45 AM

Cetuximab with or without chemotherapy for recurrent, unresectable squamous cell carcinoma of the skin (SCCS).

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Background: With an increasing aging population and a growing number of people with organ transplant on immune suppression, patients presenting with locally advanced, unresectable and metastatic SCCS are on the rise. Options of therapy are limited to platinum or taxane doublets but the tolerability of these regimens is poor. Data regarding use of cetuximab in advanced SCCS is scarce and consists of a few case series and one phase II trial. The purpose of this study is to evaluate the use of cetuximab alone or in combination with chemotherapy in patients with SCCS treated at the University of Iowa Hospitals (UIHC). **Methods:** Patient data was compiled through medical record review of all patients diagnosed with locally recurrent, unresectable or metastatic SCCS seen at UIHC and treated with cetuximab alone or in combination with chemotherapy. Pathology was centrally reviewed. **Results:** A total of nine patients with SCCS received cetuximab as part of a definitive or palliative therapy with a loading dose of 400 mg/m2 followed by weekly 250mg /m2.Median age of patients is 64. Four patients had locally recurrent or unresectable disease, and five had distant metastases. Three patients had prior history of organ transplant. Chemotherapy included carboplatin AUC 5 with 5 fluorouracil 1000mg/m2/day for four days in two patients and weekly paclitaxel 80mg/m2 in four patients. One patient received concurrent definitive radiation with 6600 cGy. In total, six patients completed at least 6 weeks of cetuximab. All these patients showed clinical improvement in pain, tumor ulcer and bleeding as compared to pretreatment. Median time to disease progression after stopping treatment was 3 months. Three patients could not complete 6 weeks of cetuximab due to disease progression. The most common side effect was skin rash and hypomagnesemia. **Conclusions:** Cetuximab alone or in combination with chemotherapy is well tolerated and does show promise in treatment of patients with unresectable or metastatic SCCS. Most common side effect was skin rash. A larger trial with longer follow up is warranted to establish the role of cetuximab and an optimal combination therapy in improving quality of life in this patient population.

9091 General Poster Session (Board #52A), Sat, 8:00 AM-11:45 AM

Targeting BET proteins in melanoma: A novel treatment approach.

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Background: Manipulation of key epigenetic regulators in melanoma proliferation is emerging as a new therapeutic strategy. Bromodomain-containing proteins such as the extraterminal domain (BET) family are components of transcription factor complexes and determinants of epigenetic memory. We investigated the expression of BRD4, a BET family member in melanoma cell lines and tissues, and the effects of its inhibition with the small molecule compounds MS436 and MS417 in in vitro and in vivo models of melanoma. **Methods:** BRD2 and BRD4 expression were analyzed by immunohistochemistry. We tested the effects of pharmacological or RNAi-mediated inhibition of BRD4 in melanoma cells using crystal violet-based assays for proliferation/colony formation and flow-cytometry for cell cycle analysis. The molecular effects of BRD4 suppression were examined using RNA sequencing, Real-Time quantitative PCR and western blots for p27, p21, MYC, ERK1 and SKP2. In the in vivo xenograft experiments NOD/SCID/IL2γR-/-mice were injected with melanoma cells and treated with MS417. Statistical significance was determined by unpaired t-test (GraphPad). **Results:** BRD4 was found significantly upregulated in primary and metastatic melanoma tissues compared to melanocytes and nevi ($p<0.001$). Treatment with BET inhibitors impaired melanoma cell proliferation in vitro and tumor growth and metastatic behavior in vivo, effects that were mostly recapitulated by individual silencing of *BRD4*. Rapidly after BET displacement, key cell cycle genes (*SKP2, ERK1* and *c-MYC*) were downregulated concomitantly with the accumulation of CDK inhibitors (p21, p27), followed by melanoma cell cycle arrest. BET inhibitor efficacy was not influenced by *BRAF* or *NRAS* mutational status. **Conclusions:** Our results demonstrate for the first time a role for BRD4 in melanoma maintenance and support the role of BET proteins as novel targets in melanoma. Further investigation in the clinical setting is warranted.

9092 General Poster Session (Board #52B), Sat, 8:00 AM-11:45 AM

Frequency of BRAF V600E variant in circulating free DNA compared with the single melanoma biopsy.

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Background: To select melanoma patients for treatment with BRAF inhibitors, the BRAF mutational status is determined in the most recent tumor biopsy. However, tumor specimens are not always available for the analysis, and relying on a single biopsy specimen can potentially exclude from treatment patients with heterogeneity among metastatic tumors due to polyclonality of BRAF mutation, which appears as a rather common condition. As an alternative approach we explored a blood-based mutation detection assay. **Methods:** We developed a method including enrichment for the BRAV600E variant by selective elimination of the wild type allele by TspRI digestion and BRAFV600E detection by TaqMan Mutation Detection Assay (BRAF_476_mu, Life Technologies). Sensitivity testing showed that BRAFV600E variant was detected starting from $6.25X10^{-5}$ ng of DNA, and specificity testing showed that the variant can be detected when diluted in $8X10^{5}$ copies of wild-type alleles. **Results:** Mutational analysis performed by Sanger sequencing of exon15 in 114 melanoma biopsies showed that 4 (3%) harbored the c.1798_1799GT>AA (V600K) mutation, 1 (1%) the c.1799_1800TG>AA mutation (V600E), and 56 (49%) the most common c.1799T>A mutation (V600E), while by the novel method the latter mutation was detected in 9 additional specimens (8% increment) and confirmed by sequencing the PCR product after TspRI digestion. Pre-surgery plasma was available for 50/114 patients at advanced stages, 26/50 (52%) showing a mutated specimen, including 4 with a double nucleotide substitution (V600K and V600E). The matched plasma samples resulted mutated in 25/26 cases with mutated biopsy and in further 14/25 samples with biopsy resulting wild type; in contrast, plasma of 50 healthy controls tested negative. Taken together, these results indicate that V600E circulating variant was detectable in 39/50 (78%) plasma samples and in 22/50 (44%) tumor specimens. **Conclusions:** Detection of BRAF V600E variant in circulating free DNA may represent a more sensitive approach for patient selection and decision making process during the treatment with BRAF inhibitors.

9093 General Poster Session (Board #52C), Sat, 8:00 AM-11:45 AM

Metastatic melanoma patients: Prospective follow-up of pigmented lesions under vemurafenib by digital dermoscopy.

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Background: Vemurafenib is the first approved by the FDA BRAF V600 inhibitor for the treatment of metastatic melanoma. Many cutaneous side-effects such as squamous cell carcinoma, xerosis, photosensitivity are observed. We first reported the occurrence of second primary melanomas (SPM) under BRAF inhibition. These SPM were shown to be wild-type for BRAF. The exact occurrence of these changes is still unknown. We wanted then to explore prospectively the impact of vemurafenib on cutaneous pigmented lesions using sequential digital dermoscopy. **Methods:** We registered prospectively following inform consent the pigmented lesions of patients under vemurafenib. We examined the total body surface and captured from 9 to 134 pigmented lesions on 24 patients. Each single lesion was followed monthly from vemurafenib initiation to vemurafenib disruption due to disease progression. Dermoscopic modifications of the melanocytic lesions including external diameter, dermoscopical pattern, pigmentation, network thickness, dots distribution and keratosis appearance were analyzed. **Results:** The median duration of dermoscopic follow up was 6,9 months (range from 2 to 16 months), 1098 pigmented lesions were included. At least one modification occurred in 56% of the lesions. Most frequent modifications were the occurrence of dark globules (56%), change in the pigmentation coloration (47%), variations in network thickness (32%), increase of the external size (20,1%), onset of black areas (14%), onset of keratosis (4,4%). Up to 5,3% of lesions spontaneously disappeared; 21 excisions were performed due to significant dermoscopic changes and revealed 10 early melanomas in 5/24 patients (20,8%). The 11 remaining lesions were benign. **Conclusions:** More than fifty percent of the patients under vemurafenib will experiment significant modifications on their pigmented lesions. In our experience 10/21 removed lesions were early melanomas that could not be otherwise diagnosed using naked-eyes examinations only. Digital dermoscopy is one of the tool that can be use to discriminate earlier the modifications. Such careful monitoring will improved the safety when evaluating BRAF inhibitors in adjuvant setting.

9094 **General Poster Session (Board #52D), Sat, 8:00 AM-11:45 AM**

Activity of cabozantinib in metastatic uveal melanoma: Updated results from a phase II randomized discontinuation trial (RDT).

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Background: MET and VEGF signaling are implicated in angiogenesis, invasion, and metastasis, and upregulation of MET as a consequence of GNAQ/GNA11 mutation has been implicated in uveal melanoma. Historical rates of median overall survival (OS) in patients (pts) with metastatic uveal melanoma range from 6-9 months (mos). A RDT evaluated activity and safety of cabozantinib, a MET and VEGFR2 inhibitor, in 9 tumor types including a metastatic melanoma cohort where 55% and 5% of pts experienced objective tumor regression and confirmed partial response, respectively (J. Clin. Oncol. 30, 2012 (suppl; abstr. 8531)). Here we report on the longer term followup of metastatic uveal melanoma pts enrolled to this cohort. **Methods:** Eligible pts were required to have progressive measurable disease per RECIST. Pts received cabozantinib at 100 mg po qd over a 12 wk Lead-in stage. Tumor response (mRECIST) was assessed q6 wks. Treatment $\geq$ wk 12 was based on response: pts with PR continued open-label cabozantinib, pts with SD were randomized to cabozantinib vs placebo, and pts with PD discontinued. Pts were followed for overall survival. **Results:** 23 of 77 pts enrolled in the melanoma cohort had the uveal subtype. Median age was 65 yrs; median prior regimens was 1 (range 0-5). Tumor mutation status was determined for 10/23 pts. 9/10 harbored either a GNAQ or GNA11 mutation, while GNA11 status was unknown for one pt. Pts had substantial tumor burden; median sum of the longest diameter of target lesions was 11.9 cm (range, 2-37.2). Median follow-up was 26.5 mos. (range 21.7-33.8). Median PFS from Study Day 1 was 4.8 mos. The estimate of PFS at month 6 (PFS6) was 41% and median OS was 12.6 mos. Most common Grade 3/4 AEs were HTN (13%), abdominal pain (9%), hypokalaemia (9%), hyperbilirubinaemia (9%) and increased lipase (9%). **Conclusions:** Cabozantinib is active in pts with metastatic uveal melanoma. Treatment with cabozantinib is associated with encouraging progression-free and overall survival. The safety profile of cabozantinib was comparable to that of other VEGFR TKIs. A randomized Phase 2 study is planned comparing cabozantinib to temozolomide plus dacarbazine in pts with uveal melanoma. Clinical trial information: NCT00940225.

9095 General Poster Session (Board #52E), Sat, 8:00 AM-11:45 AM

Identification of functional DNA methylation aberrations associated with outcome in melanoma patients with brain metastasis.

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Background: Brain metastasis (MBM) represents one of the most significant causes of death in melanoma patients. Identification of clinically relevant markers is necessary to recognize patients with high risk of MBM development. Alterations in DNA methylation patterns have been recognized as a major epigenetic hallmark of metastasis initiation and progression. **Methods:** To generate a comprehensive genomic DNA methylation landscape of MBM, we performed genome-wide data integrative analyses examining the DNA methylation (Illumina HumanMethylation 450K), gene expression (Affymetrix HumanExon 1.0), and genotype (Affymetrix SNP 6.0) of specimens related to melanoma progression from normal to MBM (n=65). **Results:** We observed significant genome-wide hypomethylation and CpG island hypermethylation according to melanoma progression to the brain. To identify significant differentially methylated CpG sites between lymph node metastasis and MBM, we applied a strict statistical threshold (β-value difference >0.3 and FDR-corrected $p < 0.005$). We identified the homeobox D (HOXD) gene family members amongst the most significantly affected genes. The influence on gene expression and the frequency of HOXD hypermethylation were verified using integrative analysis of publicly available data generated from 168 melanoma specimens. In a cohort of clinically annotated melanoma patients (n = 159), we demonstrated that hypermethylation of a genomic region in the HOXD gene cluster was significantly associated with shorter disease-free survival ($p = 0.004$) and overall survival ($p = 0.002$).Multivariate analysis confirmed the association with poorer survival ($p = 0.01$ and HR = 2.8; CI95%: 1.3-6.1). **Conclusions:** The use of genome-wide DNA methylation, gene expression, and genotyping integrative analyses allowed the identification of novel markers with functional and clinical implications for melanoma patients with brain metastasis.

9096 General Poster Session (Board #53A), Sat, 8:00 AM-11:45 AM

Assessment of absolute lymphocyte count (ALC) as a predictor of progression-free survival (PFS) and overall response rate (ORR) in metastatic melanoma (MM) patients (pts) treated with high-dose interleukin-2 (HD IL-2).

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Background: HD IL-2 is an approved immunotherapy that can achieve durable cures in MM pts. Due to toxicity and low ORR, identification of predictors of clinical benefit would enhance pt selection and outcomes with HD IL-2. Recent research identified a positive correlation for ALC $\geq$ 1000 (either at baseline or at dose 3) with OS among MM pts treated with the immunotherapy agent ipilimumab. We tested the hypothesis that ALC ($\geq$ 1000) or other hematological parameters correlates with clinical benefit from HD IL2. **Methods:** Results of hematologic testing in patients (n=98) treated with HD IL2 at MD Anderson Cancer Center were collected, including absolute levels of neutrophils (ANC), lymphocytes (ALC), monocytes (AMC), eosinophils (AEC), and platelets (APC) at baseline, after cycle 1 (C1), and after cycle 2 (C2) of HD IL-2; changes in each parameter for each interval were also calculated. Hematologic values were assessed as categorical (for ALC, $\geq$ 1000 Yes/No; other parameters, above upper limit of normal [ULN] Yes/No) and continuous variables. Associations between these parameters and PFS and ORR were analyzed. **Results:** ALC was$\geq$ 1000 in 75 pts (76%) at baseline, in 81 (83%) after C1, and in 80 of 86 pts (93%) after completion of C2 of HD IL-2. PFS was not significantly associated with ALC $\geq$ 1000 at baseline (HR 0.69, p=0.13), after C1 (HR 1.32, p=0.33), or after C2 (HR 1.01, p=0.98). ALC $\geq$ 1000 at each timepoint was not significantly associated with ORR or OS. There was no significant difference in the change in ALC with HD IL2 treatment among responders versus non-responders. Among baseline hematological factors, APC $>$ ULN was significantly associated with PFS (p=0.001), but it was rare (2/98 patients). Exploratory analyses identified significantly shorter PFS for patients with baseline APC $>$ 300 (11%, HR 2.75, p=0.002). Analysis of hematologic factors as continuous values identified significant associations with PFS for AMC (HR 2.42, p=0.03) and AEC (HR 1.73, p=0.009) after C2. **Conclusions:** ALC $\geq$ 1000 did not correlate with PFS, ORR, or OS with HD IL-2 therapy in this cohort of metastatic melanoma pts.

9097 **General Poster Session (Board #53B), Sat, 8:00 AM-11:45 AM**

What is the behavior of Breslow's thickness?

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Background: Localized cutaneous melanomas (CM) have their clinical course predicted by microscopic findings in the tumor specimen, mostly Breslow's thickness (BTL), ulceration and mitoses. It is not certain whether BTL has a linear relationship with overall survival (OS) or relapse-free survival (RFS). The aim of this study was to evaluate BTL´s linear (LC) and its non-linear component (NLC) with relation to survival. **Methods:** All consecutive cases of CM treated from 1997 to 2006 at a single institution were identified, individuals with stage I or II tumors, minimum follow up of one month and known BTL were selected, socio-demographic data, clinical and pathological findings, treatment and outcomes were abstracted. Information about ulceration was missing in more that 30% of cases and it was not evaluated, there was no information about mitotic rate. Survival was estimated by the Kaplan-Meier method. Multivariate analyses were performed by the Cox model. BTL was evaluated as a continuous variable, and the LC and NLC by the technique of smoothing, using p-splines. **Results:** There were 1465 cases of CM, 51 with no follow up, 137 had no information about BTL and 202 had advanced stages. This analysis is based on 1075 cases. In the Cox model, the variables associated OS were age [hazard ratio (HR) 1.02, 95% CI 1.01 to 1.03], sex (HR 1.56, 95% CI 1.2 to 2.04) and BTL (HR=1.079, 95% CI 1.065 to 1.094). The variables associated with RFS were age (HR 1.017, 95% CI 1.009 to 1.024), sex (HR 1.372, 95% CI 1.104 to 1.704) and BTL (1.068, 95% CI 1.057 to 1.080). In the analysis of LC and NLC of BTL, it was found that both LC and NLC were statistically significant for OS and RFS. There was an increase in the HR as BTL increased in those lesions thinner than 4mm, then such increase was not as evident and lesions with more than 10mm had a similar OS and RFS (plateau). **Conclusions:** BTL is one of the most powerful prognostic criteria of patients with stage I and II CM. The risk of death increases linearly for thin lesions up to 4mm, lesions thicker than 10mm behave as a uniform group with no further decrease in OS or RFS as the lesion becomes larger. In conclusion, BTL may not behave as a linear function, it has a LC for thinner lesions, but for thicker lesions, above 10mm, further increase in BTL may add no more risk.

9098 General Poster Session (Board #53C), Sat, 8:00 AM-11:45 AM

Melanomas of the head-and-neck skin with mutation BRAF-V600K or BRAF-V600R define a melanoma subtype with particular clinical features.

Hans Starz, Justin Moody, Julia Welzel, Christian J Haas; Klinikum Augsburg, Augsburg, Germany; Van Hall Larenstein University, Leeuwarden, Netherlands

Background: "Malignant melanoma" is a melting pot of diverse melanocytic tumor entities, which arise in different organs under varying pathogenetic circumstances. Chronic sun exposure is a major factor for the development of cutaneous melanomas of the head-and-neck (HN) region. **Methods:** 131 patients with metastatic cutaneous melanomas were included in a monocentric retrospective study. The HN skin was the primary tumor site in 41 patients. The mutational hotspots of BRAF and NRAS were analysed by Sanger sequencing. In BRAF and NRAS wildtype cases, additionally exons 11, 13 and 17 of the KIT gene were investigated. HN patients with the mutations BRAF-V600K or BRAF-V600R were defined as group A (n = 11), those with other mutations or wildtype as group B (n = 30). A and B were compared with regard to the emergence of different categories of metastases, using the Kaplan-Meier method and log rank tests. The average follow-up time was 50 months. **Results:** BRAF-V600K occurred in 10 of the 41 HN patients and in 2 of the 90 non-HN patients (p = 0.003 by T-test), BRAF-V600R in 1 HN and in 1 non-HN patient. KIT mutations were restricted to 2 HN patients. Inversely, NRAS mutations were rare in the HN (3 of 41) versus the non-HN (26 of 90) cohort (p = 0.001). Lymphatic metastasis became apparent in each of the 11 group A patients not later than 35 months after the diagnosis of the respective primary melanoma. 5 out of the 8 group A patients, who underwent sentinel node biopsies (SNB), had nodal micrometastases. During follow-up, regional nodal macrometastases emerged earlier and at a higher rate in group A compared to B (p = 0.044 by log rank test). The same applied even more significantly for satellite/intransit metastases (p = 0.002), whereas for distant metastasis no significant difference was found. **Conclusions:** BRAF-V600K/R mutations in HN melanomas define a distinct melanoma subtype with an especially high risk of lymphatic metastasis. Clinical implications may be mutation analyses already for primary HN melanomas, and SNB even for thin melanomas of this subtype. Extra-guidelines should be considered for the monitoring of these patients. Special attention to this subgroup is also necessary in clinical trials.

9099 **General Poster Session (Board #53D), Sat, 8:00 AM-11:45 AM**

Analysis of stage of melanoma diagnosis in relation to insurance type and income as indicator of early/late diagnosis.

Peter Makram Lamie; Creighton University, Omaha, NE

Background: This study compares the average stage of diagnosis for melanoma by insurance status and household income. This is the largest such study for melanoma to date. **Methods:** Using the National Cancer Database we examined 299K patients with melanoma between 2000 and 2009 at 1,408 hospitals. The relationship of average stage of diagnosis is compared across insurance types and by income for 293K patients. **Results:** The VA patients had the lowest average stage of diagnosis 0.8 with the Medicaid population exhibiting the highest 1.8. The VA was lower than Tricare which had an average diagnosis of 1.1, private insurance 1.2, Medicare 1.3, and uninsured 1.7. The lowest rate of stage IV was private insurance 3.3%, Tricare 3.6%, VAH 4.4%, Medicare 5.7%, uninsured 10%, and the highest rate was among Medicaid 14.3%. The highest income category ≥$49K had the lowest average stage at diagnosis of 1.1 compared to $39K to $48K 1.2, $33K to $38K 1.3, $28K to $32K 1.4, and <$28K had the highest average stage of diagnosis 1.4. Stage IV rate increased from the highest income 3.6%, $39K to $48K 4.6%, $33K to $38K 5.1%, $28K to $32K 5.8%, and <$28K 6.9%. Data available. **Conclusions:** VA, higher income and private insurance had earlier stage of melanoma compared to uninsured and Medicaid who had higher frequency of stage IV disease.

Insurance type	Stage					Weighted average Stage of diagnosis	P value of average stage of diagnosis	Totals	
	0	I	II	III	IV			N	%
Veterans affairs	3,758	3,068	823	422	377	0.89		8,448	2.82%
	44.48%	36.32%	9.74%	5.00%	4.46%			100%	
Tricare/military	1,017	1,813	401	309	135	1.11	<0.0001	3675	1.23%
	27.67%	49.33%	10.91%	8.41%	3.67%			100%	
Private insurance	36,952	89,811	21,346	16,183	5,623	1.20	<0.0001	16,9915	56.79%
	21.75%	52.86%	12.56%	9.52%	3.31%			100%	
Medicare	24,312	42,255	21,025	10,308	5,965	1.34	<0.0001	103,865	34.71%
	23.41%	40.68%	20.24%	9.92%	5.74%			100%	
Uninsured	952	3080	1324	1290	748	1.70	<0.0001	7,394	2.47%
	12.88%	41.66%	17.91%	17.45%	10.12%			100%	
Medicaid	751	2,161	946	1,210	849	1.87	<0.0001	5,917	1.98%
	12.69%	36.52%	15.99%	20.45%	14.35%			100%	
Total	67,742	142,188	45,865	29,722	13,697			299,214	100.00%
	22.64%	47.52%	15.33%	9.93%	4.58%			100%	

P value based on student t-statistic calculated for weighted average stage of diagnosis. VA is the comparison category.

9100 General Poster Session (Board #53E), Sat, 8:00 AM-11:45 AM

Detection of *DDR2* mutations in malignant melanoma: A potentially targetable feature of advanced stage disease.

Yongbao Wang, Shere S Billouin-Frazier, Justin P Windham, Daniel Jones; Quest Diagnostics Nichols Institute, Chantilly, VA

Background: The discoidin domain receptor tyrosine kinase 2 (*DDR2*) gene is mutated in a subset of non-small cell carcinoma of the lung. In lung cancer, targeting of DDR2 with the inhibitor dasatinib has been shown to inhibit *DDR2*-mutated cell line growth. Responses to dasatinib in *DDR2*-mutated lung tumors are currently being investigated in clinical trials. We investigated whether somatic DDR2 mutations also occur in melanomas using a set of different clinical subtypes bearing a variety of melanoma-associated molecular alterations. **Methods:** DNA was extracted from macrodissected FFPE sections of 168 melanomas and subjected to next-generation sequencing using a custom-designed 36-amplicon panel including the coding regions of *DDR2* and exons 11 and 15 of *BRAF*. PCR products were prepared by Access Array, sequenced on the Ion Torrent PGM, and analyzed using Sequence Pilot software. All *DDR2* mutations were confirmed by bidirectional Sanger sequencing. Relative expression analysis of the *DDR2* gene was performed using RT-PCR on RNA extracted from FFPE sections, with levels normalized to *ABL1* and *GAPDH*. **Results:** Heterozygous *DDR2* point mutations were identified in 3.4% of *BRAF*-mutated melanoma (n=117) but not in any cases that lacked *BRAF* mutations (n = 51). All *DDR2*-mutated melanomas were advanced stage with lymph node and/or extensive soft tissue involvement and included both *BRAF* V600K and V600E cases. In contrast to the range of mutation sites reported in lung cancers, *DDR2* mutations in melanoma (I488S, F574C, S667F and L701F) were at highly evolutionarily conserved positions in the kinase domain. The mutations are expected to be disruptive and may therefore modulate kinase activity. DDR2 transcripts were expressed in tumor cells in all mutated cases. **Conclusions:** *DDR2* mutations in advanced stage melanoma may provide a targetable genetic feature for tyrosine kinase inhibitors such as dasatinib. The invariant association of *DDR2* mutation with activating *BRAF* mutations suggests synergy in transformation between these distinct signaling pathways.

9101 General Poster Session (Board #53F), Sat, 8:00 AM-11:45 AM

Impact of complete lymphadenectomy in stage I melanoma: SEER analysis, 2004-2009.

Victoria Stager, Elizabeth Anne Arena, Joslyn Albright, Mark B. Faries; John Wayne Cancer Institute, Santa Monica, CA

Background: Stage I melanoma has excellent prognosis, yet it remains a treacherous entity leading to fatal disease progression in a small and ill-defined population of patients. Role of complete lymphadenectomy in early melanoma is not determined. **Methods:** We used the Surveillance Epidemiology and End Results (SEER) database from 2004 to 2009 to identify patients who underwent wide local excision (WLE) with or without nodal surgery for management of AJCC Stage I primary cutaneous melanoma. Patients with complete data on age, race, sex, and primary tumor histology and anatomic site were categorized by type of surgical treatment into WLE, WLE+sentinel node biopsy (SNB), or WLE+complete lymphadenectomy (CLND) groups. Five-year disease-specific survival (DSS) was determined by treatment group and by sentinel node status. Specific risk factors were identified using multivariate analysis. **Results:** During the selected time period, 51,573 patients were diagnosed with AJCC Stage I cutaneous melanoma. Rate of SNB was 22%, and out of this group, 2% of patients had metastases to the regional lymph nodes. Five-year DSS was decreased in the node-positive group compared to the patients who had a negative SNB or WLE only (HR=4.95). Rate of CLND was 67%, and it did not improve survival of the patients with positive SNB (5-year DSS 83% vs. 79%, p=0.29). Performance of CLND did not correlate with age, histological type, presence of ulceration, or Breslow depth. **Conclusions:** SEER database suggests that a clinical equipoise regarding the utility of CLND in patients with positive SLN remains. These findings justify ongoing MSLT II.

9102 General Poster Session (Board #53G), Sat, 8:00 AM-11:45 AM

Relationship of bleeding to pathologic ulceration in a primary melanoma lesion.

Paul T Kang, Amy Louise Baker, James Warneke, Clara N Curiel, Joanne M. Jeter, Evan Hersh, Lee D. Cranmer; University of Arizona Cancer Center, Tucson, AZ

Background: Lesion bleeding (BL) is a catalyst symptom leading to melanoma (MEL) diagnosis and is associated with adverse outcomes. The pathophysiologic significance of BL has not been elucidated. We hypothesize that BL reflects pathologic ulceration (UL). **Methods:** This retrospective cohort study was conducted using data from 850 patients seen 2005-2009 at our center. Eligible patients reported the pre-diagnosis BL status of their primary lesion; determination of its UL status was also required. Demographic, clinical, pathologic and outcomes data were abstracted from records. X^2 and independent t-tests were used for univariate comparisons. Predictors of UL were analyzed with multiple logistic regression. Survival indices were analyzed by the Kaplan-Meier, log-rank, and Cox proportional hazards. **Results:** 190 patients with 193 MEL lesions were eligible. Median follow-up was 5.3 yr. 67 lesions bled prior to diagnosis; 68 demonstrated UL. BL and UL were associated with each other and with Breslow depth in univariate analyses; UL was also associated with age at diagnosis. Neither was associated with gender, lesion site, use of BL-associated drugs or Clark's level. A logistic model was developed using BL, gender, lesion site, use of BL-associated drugs, and age at diagnosis. Only BL and age at diagnosis were associated with UL probability (OR=10.6/p<0.001 and OR=1.04/p=0.006, respectively). BL was associated with worsened median relapse-free (RFS) and overall survival (OS) (median 1.16y vs. 1.96y, p=0.001 and 3.06 y vs. 3.41y, p=0.001), as was ulceration. When status of BL and UL were considered together, only UL predicted outcomes. A Cox model of clinical factors (BL, gender, age at diagnosis, lesion site) confirmed the association of BL with RFS and OS (HR 1.82/p=0.006 and HR 2.36/p=0.001). Addition of UL to the model abrogated BL's predictive value. **Conclusions:** BL of primary MEL lesions is strongly associated with pathologic UL. When clinical parameters are considered, BL significantly predicts RFS and OS, although this value is lost once UL status is known. Our data are consistent with BL's reflecting the ulceration status of a primary lesion. When UL status is unknown, BL may be able to serve as its surrogate marker.

TPS9103 General Poster Session (Board #53H), Sat, 8:00 AM-11:45 AM

CA184-240: A single-arm, open-label phase II study of vemurafenib followed by ipilimumab in patients with BRAF V600-mutated advanced melanoma (AM).

F. Stephen Hodi, Asim Amin, Yvonne M. Saenger, Gregory K. Pennock, Troy H. Guthrie, April K. Salama, Lawrence E. Flaherty, Henry B. Koon, David H. Lawson, Montaser F. Shaheen, Agnes Balogh, Cyril Konto, Steven O'Day; Dana-Farber Cancer Institute, Boston, MA; Levine Cancer Institute, Charlotte, NC; Mount Sinai School of Medicine, New York, NY; M. D. Anderson Cancer Center, Orlando, Orlando, FL; Baptist Cancer Institute, Jacksonville, FL; Duke Cancer Institute, Durham, NC; Wayne State University School of Medicine, Detroit, MI; University Hospitals of Cleveland, Cleveland, OH; Emory University School of Medicine, Atlanta, GA; University of New Mexico Cancer Center, Albuquerque, NM; Bristol-Myers Squibb, Braine-l'Alleud, Belgium; Bristol-Myers Squibb, Wallingford, CT; The Beverly Hills Cancer Center, Beverly Hills, CA

Background: Ipilimumab (Ipi), a fully human monoclonal antibody that binds to cytotoxic T-lymphocyte antigen-4 expressed on T cells, and vemurafenib (Vem), a small molecule inhibitor of BRAF V600-mutated kinase, are both approved treatments for AM. Ipi has shown improved overall survival (OS) in two randomized phase III trials of patients with previously treated (3 mg/kg monotherapy) and previously untreated (10 mg/kg plus dacarbazine) AM. Vem has shown improved OS in a randomized phase III trial of patients that harbor the BRAF V600E mutation. The most common drug-related adverse events (AEs) with Ipi monotherapy were immune-related GI tract and skin toxicities, which were generally manageable using treatment guidelines. The most common AEs with Vem were arthralgia, rash, and fatigue. Vem can induce rapid and substantial responses, and resistance mechanisms are a focus of current investigation. This study will evaluate the safety of Vem lead-in followed by Ipi (prior to resistance) in patients with BRAF V600-mutated AM. **Methods:** An estimated 45 patients will be enrolled. Eligible patients include those $\geq$18 years old with previously untreated AM, a BRAF V600 mutation, and an ECOG PS of 0 or 1. Major exclusion criteria are primary ocular melanoma, active brain metastases, and autoimmune disease. Patients will initially receive Vem for 6 weeks (960 mg twice daily). After a washout period of 3-10 days (per protocol), patients will be initiated on Ipi at 10 mg/kg (every 3 wk for 4 doses, then once every 12 wk beginning at week 24, until disease progression or unacceptable toxicity). Vem will be restarted at the time of disease progression on Ipi (no minimum time to restart) or unacceptable toxicity on Ipi (restart minimum of 1 mo after the last dose of Ipi). Vem will be restarted at the last dose level tolerated at the end of the lead-in phase. Patients will be followed every 12 weeks for toxicity and/or disease progression, and subsequently will be followed every 12 weeks for survival. The objectives of this study are to estimate the incidence of grade 3-4 drug-related AEs. Exploratory objectives include the evaluation of efficacy (OS). Clinical trial information: NCT01673854.

TPS9104 General Poster Session (Board #54A), Sat, 8:00 AM-11:45 AM

Open-label, multicenter, single-arm, phase I, dose-dscalation with efficacy tail extension study of vemurafenib in pediatric patients with surgically incurable and unresectable stage IIIc or IV melanoma harboring *BRAF*^{V600} mutations (NCT01519323).

Fariba Navid, Julia C. Chisholm, Andrea Ferrari, Cynthia E. Herzog, Carlos Rodriguez-Galindo, Axel Hauschild, Kartik Krishnan, Alberto S. Pappo; St. Jude Children's Research Hospital, Memphis, TN; The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy; Division of Pediatrics, University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute/Children's Hospital, Boston, MA; University of Kiel, Kiel, Germany; Genentech, Inc., South San Francisco, CA

Background: Although rare, melanoma is the most common form of skin cancer in children and the incidence is rising in the adolescent population. Similar to adults, the outcome for pediatric patients with advanced or recurrent melanoma is poor. Many adult studies of melanoma exclude patients under the age of 18 years. Approximately 50% of melanomas carry a mutation in the *BRAF* gene and the oral BRAF inhibitor vemurafenib (VEM) has demonstrated improved rates of overall and progression-free survival in adult melanoma patients who carry this mutation (Chapman et al; *NEJM* 2011). The current study is designed to determine the maximum tolerated dose (MTD)/recommended dose (RD), pharmacokinetics, safety, tolerability, and efficacy of VEM in pediatric patients with surgically incurable and unresectable stage IIIC/IV melanoma harboring *BRAF*^{V600}mutations. **Methods:** Patients aged 12 through 17 years with newly diagnosed or previously treated measurable disease are eligible. Patients with radiographically stable, asymptomatic previously treated central nervous system lesions are also eligible. In the dose-escalation phase, patients will be enrolled sequentially to increasing dose cohorts of VEM following a 3+3 design. Dose-limiting toxicity will be assessed during the first cycle (defined as the first 28 days). The initial dose will be 720 mg BID (patients $\geq$45 kg) or 480 mg BID (patients $<$45 kg). Once the MTD/RD for the extension phase is defined based on the dose-escalation window, all patients will be eligible to receive the MTD/RD. The efficacy tail of the trial will enroll additional pediatric patients at the MTD/RD. Patients will receive VEM until disease progression, death, unacceptable tolerability, discontinuation from the study, or other protocol-specified criteria. The study aims to treat approximately 20 patients at the RD with 3-15 additional patients treated at other dose levels during the dose-escalation phase. This study is currently open at 18 sites in the USA, UK, Germany, Italy, and Australia. As of January 24, 2013, one patient has been enrolled. Clinical trial information: NCT01519323.

TPS9105^ General Poster Session (Board #54B), Sat, 8:00 AM-11:45 AM

A phase III open-label study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus investigator's choice in advanced melanoma patients progressing post anti-CTLA-4 therapy.

Bartosz Chmielowski, Omid Hamid, David R. Minor, Sandra P. D'Angelo, Gregory K. Pennock, Kenneth Grossmann, Paolo Antonio Ascierto, Adil Daud, Reinhard Dummer, F. Stephen Hodi, Céleste Lebbé, Caroline Robert, Jeffrey Alan Sosman, Arvin Yang, Alexandre Lambert, Jeffrey S. Weber; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; The Angeles Clinic and Research Institute, Los Angeles, CA; California Pacific Center for Melanoma Research and Treatment, San Francisco, CA; Memorial Sloan-Kettering Cancer Center, New York, NY; M. D. Anderson Cancer Center, Orlando, Orlando, FL; Huntsman Cancer Institute, Salt Lake City, UT; Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; University of California, San Francisco, San Francisco, CA; University of Zurich Hospital, Zurich, Switzerland; Dana-Farber Cancer Institute, Boston, MA; Hôpital Saint-Louis, Paris VII University, Paris, France; Institut Gustave Roussy, Villejuif, France; Vanderbilt-Ingram Cancer Center, Nashville, TN; Bristol-Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Braine-l'Alleud, Belgium; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Despite the recent approval of ipilimumab and vemurafenib for advanced melanoma, there is still a large unmet need for patients (pts) who have progressed on anti-CTLA-4 therapy and a BRAF inhibitor (depending on BRAF status). Programmed death-1 (PD-1) is a co-stimulation inhibitory receptor that negatively regulates T-cell activation and is upregulated in tumor-infiltrating lymphocytes. Upregulation of PD-1 is also associated with advanced disease in melanoma. Nivolumab, an anti-PD-1 receptor blocking monoclonal antibody, demonstrated durable antitumor activity in a phase 1 study in 106 pts with advanced melanoma with objective responses (OR) observed in 31% and stable disease ≥24 weeks in 6% with a manageable safety profile (Topalian SL et al; ESMO 2012 [Abstr 453P]). Here we describe a phase III study designed to compare the clinical benefit of nivolumab to chemotherapy of investigator's choice in previously treated pts with unresectable or metastatic melanoma. **Methods**: In this two arm open-label study, approximately 390 pts will be randomized 2:1 to receive either nivolumab 3 mg/kg IV every two weeks (Arm A) or either dacarbazine 1000 mg/m^2 IV or carboplatin AUC6/paclitaxel 175 mg/m^2 IV every 3 weeks (Arm B) until disease progression or treatment discontinuation. Pts included are those with ≤2 regimens for advanced melanoma who have progressed on anti-CTLA-4 therapy as well as a BRAF inhibitor if BRAF V600-mutation positive. Pts without active brain metastases are eligible. All pts require baseline fresh biopsy to determine PD-L1 expression. Pts will be stratified by tumor PD-L1 expression, BRAF status, and prior anti-CTLA-4 best response. Tumor response per RECIST 1.1 will be assessed 9 weeks following randomization and every 6 weeks thereafter for the first year. After the first year, response will be assessed every 12 weeks until disease progression or treatment discontinuation. The co-primary endpoints are overall survival (OS) and OR rate. Secondary endpoints include progression-free survival, correlation of PD-L1 expression with clinical outcome, and health-related quality of life. Clinical trial information: NCT01721746.

TPS9106 General Poster Session (Board #54C), Sat, 8:00 AM-11:45 AM

A phase III, randomized, double-blind study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus dacarbazine in patients (pts) with previously untreated, unresectable, or metastatic melanoma (MEL).

Caroline Robert, Paolo Antonio Ascierto, Michele Maio, Micaela Hernberg, Henrik Schmidt, Ian Waxman, Claus Garbe, Céleste Lebbé, Axel Hauschild; Institut Gustave Roussy, Villejuif, France; Istituto Nazionale Tumori Fondazione, Naples, Italy; University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; Helsinki University Central Hospital, Helsinki, Finland; Aarhus University Hospital, Aarhus, Denmark; Bristol-Myers Squibb, Princeton, NJ; Eberhard Karls University, Tuebingen, Germany; Hôpital Saint-Louis, Paris, France; University of Kiel, Kiel, Germany

Background: The 5-year survival rate for late-stage MEL is currently only 15%. Despite recent advances with ipilimumab and vemurafenib, a considerable unmet need remains for pts with previously untreated, unresectable or metastatic BRAF wild-type MEL. Objective response rate (ORR) with first-line dacarbazine, a widely used chemotherapy in MEL, is 13%, with median overall survival (OS) ranging from 5.6 to 11 months. Programmed death-1 (PD-1) is an immune checkpoint receptor that negatively regulates T-cell activation through interaction with its ligand, PD-L1. This ligand is overexpressed by multiple tumor types, including advanced MEL. The PD-1 receptor blocking antibody nivolumab demonstrated clinical activity at 0.1-10 mg/kg in a phase I study in pts with advanced MEL (n = 106), with OR in 33 pts and stable disease ≥24 weeks in 6 pts. We describe a double-blind, randomized phase III study designed to compare the clinical benefit of nivolumab vs dacarbazine in pts with advanced MEL. **Methods:** Approximately 410 pts with untreated, unresectable stage III or stage IV MEL will be randomized 1:1 to receive either nivolumab 3 mg/kg IV every two weeks or dacarbazine 1000 mg/m^2 IV every three weeks until disease progression or unacceptable toxicity. All pts must be BRAF wild-type as per V600 mutational testing. Pts will be stratified by PD-L1 status (positive vs negative/indeterminate) and metastatic (M) stage (M0/M1a/M1b vs M1c). PD-L1 positivity will be defined as ≥5% total membrane staining in tumor cells. Tumor response (per RECIST 1.1) will be assessed 9 weeks following randomization and every 6 weeks thereafter for the first year. After the first year, response will be assessed every 12 weeks until disease progression or treatment discontinuation. Treatment may continue beyond initial progression at the investigator's discretion for pts showing clinical benefit and tolerating therapy. The primary endpoint is OS. Secondary endpoints include progression-free survival, ORR, whether PD-L1 expression is a predictive biomarker for OS, and health-related quality of life. Clinical trial information: NCT01721772.

TPS9107^ General Poster Session (Board #54D), Sat, 8:00 AM-11:45 AM

An open-label, randomized, phase II study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) given sequentially with ipilimumab in patients (pts) with advanced or metastatic melanoma (MEL).

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Background: Programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) are immune checkpoint receptors that attenuate T-cell responses and contribute to immune evasion by tumor cells. Nivolumab is a PD-1 receptor blocking monoclonal antibody that has shown clinical activity in phase 1 trials with various tumor types including MEL. Ipilimumab is an anti-CTLA-4 monoclonal antibody approved for advanced or metastatic MEL. Preclinical data suggest that combined PD-1 and CTLA-4 receptor blockade may improve antitumor activity in MEL, with PD-1 blockade upregulating CTLA-4 expression and CTLA-4 blockade upregulating PD-1 expression on tumor-infiltrating T cells. We describe a phase II study evaluating nivolumab administered sequentially with ipilimumab in pts with advanced (unresectable stage III) or metastatic (stage IV) MEL. **Methods:** This open-label, phase II study will enroll approximately 80 pts. During the induction period, pts will be randomized 1:1 to either nivolumab (3 mg/kg, q2w) from Weeks (Wk) 1-13 followed by ipilimumab (3 mg/kg, q3w) from Wks 14-25, or ipilimumab followed by nivolumab at the same doses and schedules. All pts will then receive nivolumab (3 mg/kg, q2wk) during the continuation period until disease progression or unacceptable toxicity, for $\leq$2 years from initial study treatment. Pts may be treatment-naive or have disease recurrence or progression after one prior systemic therapy, excluding prior anti-PD-1, anti-CTLA-4, or a BRAF inhibitor. The primary endpoint is the incidence of treatment-related Grade 3–5 adverse events (AEs) during the induction period. Secondary endpoints are response rate at Wk 25 and progression rates at Wks 13 and 25. Exploratory endpoints include safety and tolerability; overall survival; pt-level time course of treatment-related grade 3–5 AEs, response, progression, treatment discontinuation, and death; the association of changes in pharmacodynamic immune markers from baseline to Wk 13 and Wk 25 and clinical response; the association between baseline immunological parameters and clinical response; and immune-related single nucleotide polymorphisms. Clinical trial information: NCT01783938.