melanoma and other skin tumors

**CLINICAL ACTIVITY AND SAFETY OF ANTI-PROGRAMMED DEATH-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) IN PATIENTS (PTS) WITH ADVANCED MELANOMA (MEL)**

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**Purpose:** BMS-936558 is a monoclonal antibody that blocks the PD-1 co-inhibitory receptor expressed by activated T cells. This study describes its activity and safety in pts with previously treated advanced MEL.

**Methods:** BMS-936558 was administered IV q2wk to pts with various tumors at 0.1 – 10 mg/kg during dose-escalation and/or cohort expansion. Pts received up to 12 cycles (4 doses/cycle) of treatment or until unacceptable toxicity, confirmed progressive disease, or complete response. Clinical activity was assessed by RECIST v1.0.

**Results:** As of Feb 24, 2012, 104 MEL pts had received BMS-936558 at 0.1 (n = 17), 0.3 (n = 19), 1 (n = 31), 3 (n = 17), or 10 mg/kg (n = 20). ECOG performance status was 0/1/2 in 62/33/8 pts, respectively. Most pts (81/104) had received prior immunotherapy (IT); prior anti-CTLA-4, PD-1, or PD-L1 was not permitted. The number of prior therapies was 1 (39%), 2 (35%), or ≥3 (26%). Median therapy duration was 20 wks (range 2.0 – 121.7 wks). The incidence of grade 3–4 adverse events was 20% and included gastrointestinal (4%), endocrine (2%), and hepatobiliary disorders (1%). There were no drug-related deaths in MEL pts. Clinical activity (responses or prolonged stable disease) was observed at all doses (Table). Of the 26/94 (28%) evaluable responders, 19 (73%) are ongoing ranging from 1.9+ to 24.9+ months. For the 23 responders followed 6 months from first dose on study, 16 (74%) are progression free. ORRs occurred in pts with visceral or bone metastases. Six decreases in target lesion tumor burden in the presence of new lesions and were not

**Conclusions:** BMS-936558 had durable clinical benefit in pts with advanced MEL, including those who had received prior IT. Additional long-term follow-up data will be reported.

<table>
<thead>
<tr>
<th>Dose, (mg/kg)</th>
<th>No. pts¹</th>
<th>ORR, No. pts (%)</th>
<th>PFSR at 24 wk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>14</td>
<td>4 (29) [8 – 58]</td>
<td>40 [13 – 66]</td>
</tr>
<tr>
<td>0.3</td>
<td>16</td>
<td>3 (19) [4 – 46]</td>
<td>51 [9 – 54]</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>8 (30) [14 – 50]</td>
<td>45 [26 – 65]</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>7 (41) [18 – 67]*</td>
<td>55 [30 – 80]</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>4 (20) [6 – 44]</td>
<td>30 [9 – 51]</td>
</tr>
</tbody>
</table>

¹CDR, *Response-evaluable pts dosed by 7/01/2011 ORR = objective response rate (CDR + PR + R) / n = 100; PFSR = progression-free survival rate.


**IMMUNOGENICITY AND SAFETY OF THE PRAME CANCER IMMUNOTHERAPEUTIC IN METASTATIC MELANOMA: PHASE I/II DOSE ESCALATION STUDY**

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**Introduction:** Patients (pts) with metastatic melanoma have a poor prognosis. The PRAME tumor antigen, expressed at high frequency in different cancers and at lower levels in a limited number of normal cells, offers an attractive target for active immunization. This open-label, dose-escalation phase I/II study aimed at determining the optimal dose of PRAME immunotherapeutic (PRAME recombinant protein (recPRAME) with AS15 immunostimulant) by evaluating its safety and immunogenicity in pts with advanced melanoma.

**Methods:** Pts with stage IV PRAME-positive melanoma were enrolled to 3 consecutive cohorts to receive up to 24 injections of recPRAME (20 µg, 100 µg, and 500 µg) with AS15 (fixed dose) over approximately 4 years. Adverse events (AEs), including pre-defined dose-limiting toxicity (DLT), were recorded throughout the study. The anti-PRAME humoral and cellular responses were evaluated post-dose 4 by ELISA and flow cytometry (PRAME-specific T-cells producing both IFNγ and TNFα), respectively.

**Results:** 66 pts were treated in the study (20 pts received 20 µg recPRAME, 24 pts received 100 µg recPRAME and 22 pts received 500 µg recPRAME). AEs considered by the investigator to be causally related were mostly grade 1/2, 2 pts reported grade 3 AEs, and 1 serious AE causally related to PRAME administration was reported. 2 DLTs were recorded in 2 pts (cohorts 2 and 3; post-dose 6 and 8) but no maximum tolerated dose was reached. Humoral and cellular immunological results are shown in table 1. No cellular response for CD8+ T-cells was detected.

**Conclusions:** PRAME cancer immunotherapeutic was well-tolerated and induced similar humoral and cellular responses in all 3 cohorts. Based on these results, a phase II was initiated to further evaluate the clinical activity, safety and immunogenicity of the PRAME immunotherapeutic containing 500 µg recPRAME.

**Immunogenicity post-dose 4 (ATP population).**

<table>
<thead>
<tr>
<th>Cohort (recPRAME dose)</th>
<th>1 (20 µg)</th>
<th>2 (100 µg)</th>
<th>3 (500 µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral responders, n/N</td>
<td>13/13</td>
<td>13/13</td>
<td>17/17</td>
</tr>
<tr>
<td>CD8+ T-cell responders, n/N</td>
<td>7/9 (79%)</td>
<td>7/11 (64%)</td>
<td>11/15 (73%)</td>
</tr>
<tr>
<td>CD8+ T-cell responders, n/N</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
</tr>
</tbody>
</table>

number of patients enrolled into each group; * number of patients with pre and post-vaccination results; n, number of responders; ATP, according-to-protocol
Background: Patients (pts) with advanced basal cell carcinoma (aBCC) disease that is locally advanced (laBCC) or metastatic (mBCC) have limited therapeutic alternatives. The Hedgehog signaling pathway is a key driver in the pathogenesis of BCC. In a pivotal Phase II study, vismodegib (Erivedge\textsuperscript{TM})—a first-in-class small-molecule inhibitor of Hedgehog pathway signaling—demonstrated significant clinical activity in aBCC with an acceptable safety profile. This US-only expanded access study initiated prior to FDA approval, provided vismodegib for aBCC pts and further characterized its safety profile and clinical activity.

Methods: Pts with histologically confirmed mBCC or laBCC inappropriate for, or recurring after surgery or radiotherapy, received daily oral vismodegib 150 mg until disease progression or untoward toxicity. Interim data on the first 96 pts, enrolled Jul 2010–Nov 2011, are summarized; final results will be presented at the meeting.

Results: Of 96 pts (52 laBCC, 44 mBCC), 74% were male; median age was 63 (28–100) years. Median disease duration from diagnosis was 3.6 (0.02–33.2) years. Prior treatments included surgery (92%) and radiotherapy (51%). Pts received vismodegib for a median of 4.3 (0.6–16.1) months (median follow-up (f-u) 4.7 [0.6–16.1] months). Treatment-emergent adverse events (AEs) of any grade in 102 pts were: muscle spasms (60.4%), alopecia (55.2%), dysgeusia (55.2%), weight decrease (48.5%), fatigue (48.5%), nausea (45.5%), diarrhea (32.3%), dyspepsia (32.3%), and weight increase (15%). The investigator-assessed response rate was 20/40 (50%; 95% CI 34–66%) for mBCC, and 16 (40%) with laBCC. Of 69 evaluable patients with RECIST-measurable disease, the investigator-assessed response rate was 20/40 (50%; 95% CI 34–66%) for laBCC and 16 (40%) with mBCC, with stable disease in 25% of pts (14/56) of mBCC with aBCC had stable disease.

Conclusions: Incidence and severity of AEs and clinical activity reported in this analysis are similar to those reported in aBCC pts with vismodegib. Vismodegib is an effective treatment option for aBCC pts.
A PHASE 2 RANDOMIZED STUDY OF RAMUCIRUMAB (IMC-1112B; RAM) WITH OR WITHOUT DACarbazine (DTIC) IN PATIENTS (PTS) WITH METASTATIC MELANOMA (MM) (CP12-0604/NCT00353702)

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Background: Vascular endothelial growth factor (VEGF)-mediated angiogenesis contributes to MM pathogenesis. RAM is a fully human IgG1 recombinant monoclonal antibody that inhibits VEGF receptor-2 (VEGFR-2) ligand binding and signaling. We investigated RAM alone and in combination with DTIC in chemotherapy-naive MM pts.

Methods: Eligible pts had stage IV cutaneous MM, ECOG PS 0-1, adequate hematologic, hepatic, and renal function. Therapy (Rx) in Arm A: RAM (10 mg/kg) + DTIC (1000 mg/m2); Arm B: RAM (10 mg/kg). Rx was every (q) 3 weeks (wk); tumor assessments were q6 wk. The primary endpoint was progression-free survival (PFS); other endpoints were safety, overall survival (OS).

Results: 106 pts were randomized; 102 received initial Rx. Arm A (n = 52) median (medn) age was 63, 71% male, 37% had elevated LDH, 23% stage Mic. Arm B (n = 50) medn age was 62, 76% male, 28% had elevated LDH. 36% Arm A had stage IVb; DFS and OS rates were 31% and 18%. Arm A (n = 26) medn age was 63, 71% male, 37% had elevated LDH, 23% stage M1c. Arm B (n = 24) medn age was 63, 76% male, 37% had elevated LDH; 38% had stage IVb. DFS and OS rates were 31% and 18%. There were 9 (17%) partial responses (PR) & 13 (27%) with stable disease (SD); 2 (4%) & 21 (42%) SD on Arms A and B, respectively. OS was 8.7m Arm A; 11m Arm B. Nonhematologic adverse events (AEs) considered at least possibly related to RAM included fatigue (50%; 4% Grade [G] ≥3), hypertension (HTN) (21%; G ≥3), infusion-related reactions (IRR) (8%; G ≥3), proteinuria (PU) (8%; G ≥3), headache (10%; G ≥3), nausea (14%; G ≥3), rash (3%; G ≥3), dyspnea (3%; G ≥3). After a median follow-up (FU) period of 20.6m Arm A and 19.3m Arm B; median PFS was 2.6m (Arm A and 1.7m Arm B; 6m PFS rates were 31% and 18%; 12m PFS rates were 24% and 16% on Arms A and B, respectively. There were 9 (17%) partial responses (PR) & 13 (27%) with stable disease (SD); 2 (4%) PR & 21 (42%) SD on Arms A and B, respectively. OS was 8.7m Arm A; 11m Arm B. Nonhematologic adverse events (AEs) considered at least possibly related to RAM included fatigue (50%; 4% Grade [G] ≥3), hypertension (HTN) (21%; G ≥3), infusion-related reactions (IRR) (8%; G ≥3), proteinuria (PU) (8%; G ≥3), headache (10%; G ≥3), nausea (14%; G ≥3), rash (3%; G ≥3), dyspnea (3%; G ≥3).

Conclusions: RAM alone or in combination with DTIC was associated with acceptable incidence of AEs in MM. Clinical activity was modest on both arms. Although the study was not powered for definitive comparison between treatment arms, PFS appeared greater in Arm A. Biomarker analysis is ongoing.

Disclosure: R. Carvajal: Consulting, Novartis - money paid to me Consulting, Morphoxt: - money paid to me Consulting, Mabphote: - money paid to me Grants, NIH/NCI - money paid to me Grants, FDA - money paid to me Grants, ASCO - money paid to me. J. Thompson: ImClone provided funding to the University of Washington to support this research. K. Lewis: National Cancer Research Funding - money paid to me Consultant, Bristol-Myers Squibb - money paid to me Consultant. J. Wolchok: Consultant - Bristol-Myers Squibb, GlaxoSmithKline Research support - Bristol-Myers Squibb and GlaxoSmithKline. P. Rojas: I am an employee of Lilly and own Lilly stock. J. Schwartz: I am an employee of Lilly and own Lilly stock. All other authors have declared no conflicts of interest.

SKIN-TEST INFLTRATING LYMPHOCYTES PREDICT CLINICAL OUTCOME OF DENDRITIC CELL BASED VACCINATION IN METASTATIC MELANOINA

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Introduction: The identification of responding patients early during treatment would greatly improve the efficacy of novel and costly immunotherapies. Biopsies which accurately link preceding immune responses to clinical outcome are therefore needed. The mainstay of immunotherapy is to induce, enhance or sustain TAA-specific effector T cell immunity. Consequently, evaluation of the migratory-, antigen recognition-, as well as the effector function of tumor-specific cellular immune responses is critical.

Methods: A large cohort of metastatic melanoma patients (n = 91) enrolled in dendritic cell (DC)-based vaccination protocols was retrospectively analyzed for overall survival (OS) in relation to skin-test infiltrating lymphocyte (SKIL) cultures characteristics. Increasingly stringent criteria were defined identify long-term survivors.

Results: The presence of TAA-specific CD8+ T cells (criterion I: detection by tetramer MHC peptide complexes) in SKIL cultures associated with improved OS; 14.1 versus 10.6 months, p = 0.055. Further analyses showed that the presence of multiple specificities was highly predictive for long-term survival. Tumor recognition by TAA-specific CD8+ T cells on peptide level (detected by specific production of Th1 (Th1) cytokines (criterion II: e.g. IFNg and/or IL-2) or cytotoxicity and no Th1 (Th2) cytokines) was strongly associated with improved OS; 14.2 versus 10.2 months, p = 0.003. Recognition of naturally processed antigen by specific production of Th1 cytokines or cytotoxicity and no Th2 cytokines (criterion III), maximized the accuracy of the test; 24.1 versus 9.9 months, p = 0.008.

Conclusion: Our results demonstrate that analyzing SKIL cultures is a solid bioassay to predict overall survival in metastatic melanoma patients. This bioassay is simple, feasible and integrates multiple aspects of cellular functions needed for effective immune responses.

Disclosure: All authors have declared no conflicts of interest.

FIVE-YEAR SURVIVAL RATES FOR PATIENTS (PTS) WITH METASTATIC MELANOMA (MM) TREATED WITH IPILIMUBAB (IMPI) IN PHASE II TRIALS

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Purpose: Two phase II/III randomized trials showed statistically significant improvement in overall survival (OS) in MM pts treated with IMPI and data from phase II/III studies of IMPI suggest the potential for prolonged survival (beyond 4 yrs) in some pts with MM. Three phase I/II studies conducted at NCI demonstrated 5-y
### Multiple Primary Melanomas from the Same Patients Present Discrepant Somatic Alterations in Main Candidate Genes

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**Background:** A series of patients with multiple primary melanoma (MPM) were screened for the involvement of the key-regulator genes in susceptibility (CDKN2A) and pathogenesis (BRAF, cKIT, CyclinD1) of such a disease.

**Methods:** Genomic DNA from peripheral blood of 63 MPM patients (54 cases with two primary melanomas, 8 with 3 and 1 with 4) were screened for germline mutations in p16CDKN2A and p14CDKN2A genes by automated DNA sequencing.

Melanoma families were identified according to standard criteria: 9 (14%) patients were classified as familial cases. Paired synchronous or asynchronous MPM tissues (N = 100) from same patients (N = 46) were analyzed for somatic mutations in BRAF gene and FISH-based amplifications in KIT and CyclinD1 genes.

**Results:** Overall, 6 (10%) different CDKN2A germline mutations were identified: 5 in p16CDKN2A and 1 in p14CDKN2A. The age of onset was significantly lower and the number of primary melanomas higher in patients with mutations. CDKN2A mutations were significantly more frequent in patients with familial history of melanoma (5/9; 56%) compared with patients without (1/54; 2%) (P < 0.001), and in patients with more than two melanomas (5/9; 55%) compared with patients with only two melanomas (3/54; 6%) (P = 0.012). The debated A14T BRAF polymorphism was found at low level (2/54; 4%) in our series. Regarding genetic alterations at somatic level, BRAF mutations were identified in 36/100 (36%) primary melanoma tissues, whereas amplification of KIT and CyclinD1 genes was observed in 2/88 (2%) and 10/88 (11%) analyzed tissue samples, respectively. Considering all types of genetic events, paired samples presented a poorly consistent distribution of somatic alterations in same patients (52% consistency).

**Conclusions:** Coexistence of MPM and familial recurrence of melanoma as well as the presence of more than two melanomas seem to be strong indications to address patients to CDKN2A mutational screening. The low consistency in genetic patterns of primary tumours from the same patients provide additional evidence that pathogenetic mechanisms of melanomagenesis are heterogeneous and molecularly different cell types may be generated in multiple primary melanoma.

**Disclosure:** All authors have declared no conflicts of interest.

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### Long Term Survival and Immunological Correlates in Metastatic Melanoma Treated with Ipilimumab at 10 mg/kg Within an Expanded Access Program

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**Background:** Ipilimumab (IPI) has shown long lasting responses in metastatic melanoma (MM) patients (pts) in phase II/III trials (Hodi et al., NEJM 2010; Robert et al. NEJM 2011; Prieto et al., CCR 2012). We have previously reported a significant clinical efficacy of IPI in 27 heavily pre-treated MM pts enrolled within the 10 mg expanded access program (EAP) available at the University Hospital of Siena, one and 2 years survival rates were 34.8% and 23.5%, respectively (Di Giacomo, et al. CII, 2010). In spite of its clinical efficacy, no definitive predictive markers of response representing predictive markers of clinical effectiveness in the daily practice.

**Methods:** With a median follow-up of 9.6 months the median OS was 9.6 months (95% CI 4.2-16.1; range 0.1-31.0) for 27, 27, 24 and 23 pts, respectively.

**Results:** With a median follow-up of 9.6 months the median OS was 9.6 months (95% CI 4.2-16.1; range 0.1-31.0; three and 4-years survival rates were 20.9%, with 5 long-term survivors (>4 years). A significant (p < 0.05) increase in the percentage and absolute number of CD4+CD8+ and CD8+CD4+ circulating T cells was observed from W7 on. Compared to baseline, pts with a fold increase in CD4+CD8+ and CD8+CD4+ T cells higher than at W7 and W12 experienced a clinical benefit (SD, PR and CR). Pts with a N/L ratio lower than median at W7 and W10 had a significantly better survival.

**Conclusions:** IPI can induce long-term survivals in heavily pre-treated MM pts. Circulating CD4+CD8+ T cells and N/L ratio in the course of treatment with IPI may represent predictive markers of clinical effectiveness in the daily practice.

**Disclosure:** M. Maio: Advisory Board and Honoraria from Bristol-Myers Squibb and Roche. Other authors have declared no conflicts of interest.
Results: The frequencies of ERp29 c.293AA > G; PTCH1 g.79755C > T and g.79466C > T polymorphisms with inherited risk of cutaneous melanoma genotyping (5.0 SNP array, Affymetrix®), and the quantities and functions of the proteins encoded by distinct alleles of the polymorphisms are being examined by our research group. Objective: We believe to verify whether the different genotypes of polymorphisms in MCC c.5077AA > G, PTCH1 g.79755C > T, and PTCH1 g.79466C > T exceed the CM susceptibility.

Materials and methods: Genomic DNA of 149 CM patients and 153 controls was analyzed by TaqMan genotyping (Applied Biosystems®). Statistical significance of difference between groups was calculated by using chi-square (χ²) and Fisher’s exact tests. Power analysis (PA) was used to verify the effect of sample size on the results obtained in the study.

Results: Samples from patients with MC and controls were in Hardy-Weinberg equilibrium for MCC and PTCH1 loci. Similar frequencies of MCC and PTCH1 genotypes were observed in patients and controls. Individuals with distinct isolated genotypes of the genes were under similar risks for CM. The frequencies of the combined genotypes MCC 5077AA + PTCH1 79755C (90.4% versus 72.3%, P= 0.004; PA: 99.0%); MCC 5077AA + PTCH1 79466C (89.0% versus 71.6%, P= 0.008; PA: 98.9%); and MCC 5077AA + PTCH1 79755C + PTCH1 79466C (91.3% versus 76.1%, P= 0.004; PA: 99.0%) were higher in patients than in controls. Individuals with these genotypes were at 4.44 (CI95%: 1.68 – 13.17), 3.60 (CI95%: 1.45 – 8.7), and 4.70 (CI95%: 1.75 – 14.63)-fold increased risks for CM than others, respectively.

Conclusion: Our data for the first time demonstrate that BT and survival decreased higher (hazard ratio, 7.44; 95% CI, 3.27-16.93) in patients with low SES living alone. SES correlated with time from onset of symptoms and surgical resection in stage I-II primary cutaneous melanoma. A total of 1274 available pts were analyzed. Overall a progressive decrease of BT was observed (table 1). In the first four year period gender and age correlated with middle vs high OR (95%CI): 1.86 (1.05-3.31), respectively. Finally compared with low SES patients. These pts should be considered the optimal conclusion:

All authors have declared no conflicts of interest.
high response rates and prolonged progression-free survival. These results emphasize the importance of molecular information, even in those cases in which the diagnosis is made on small samples obtained through minimally invasive approaches. Cytology is an accurate and cost-effective tool for the diagnosis of MM and cytological smears are occasionally the only samples available from these patients.

**Methods:** We have studied BRAF and c-KIT mutations in 62 cytological samples from MM patients. Preliminary results of 56 cases (32 men (58%) and 23 women (42%); median age 52 years) are included in this abstract. Diagnosis was made on fine needle aspiration in 41 cases, imprint in 10, direct eye touch in 1, a smear from cellular culture in 1, and pleural and peritoneal fluid in 3. To assure tissue quality, DNA was extracted directly from Papanicolaou stained smears on which cytological diagnosis was made. BRAF and c-KIT mutations were analysed by PCR and direct sequencing using an ABI PRISM TM 310XL.

**Results:** BRAF mutations were found in 30 cases (53.5%): V600E mutation in 26 (86.7%) and V600K in 4 (13.3%). c-KIT mutations were studied in 18 cases. L576P mutation was present in 1 patient with liver metastasis from acral melanoma (5.56%). BRAF status did not correlate with primary melanoma histology, age at diagnosis, disease free survival, brain metastases rate and overall survival.

**Conclusions:** The frequency of activating mutations in BRAF is 53.5% in this series. V600E is the most commonly observed mutations, but V600K appears in 13.3% of the cases. c-KIT mutations incidence is low (5.56%). Mutational analysis of BRAF and c-KIT using cytological samples from patients with metastatic melanoma is feasible and can be used to extend the benefits of targeted therapy to those patients from which biopsies are not available. Updated results will be presented.

**Disclosure:** S. Martin-Algarra: Participation in Advisory Boards of Roche. All other authors have declared no conflicts of interest.
12 and repeated every 4 weeks until disease progression or unacceptable toxicity occurred. The primary endpoint was progression-free survival (PFS) rate at 6 months. Responses were evaluated using immune-related response criteria.

Results: Sixty-four pts were enrolled and received at least one dose of study drug. All pts were included in the analysis. With a median follow-up of 51 weeks, the PFS rate at 6 months was 45%, exceeding the proposed rate of 30%, and the median PFS was 22 weeks. There were 10 (15.6%) confirmed complete responses and 10 (15.6%) confirmed partial responses. To date, median overall survival has not been reached. Among many variables including age, gender, ECOG PS, and stage, there was a statistically significant difference in PFS in the group of patients with bone metastasis and those without bone metastasis.

Conclusion: At a median follow-up of 51 weeks, the overall response rate in this study is 31%. Ipilimumab at 10 mg/kg in combination with tem did induced in an induction followed by maintenance fashion is safe, well-tolerated, and efficacious in MM. The primary endpoint of 6-month PFS has been reached and exceeded.

Disclosure: S. Patel: Research funding from Bristol-Myers Squibb. W. Hwu: Research funding from Merck Research funding from Bristol-Myers Squibb. K. Kim: Research funding from Bristol-Myers Squibb Advisory board, honoraria from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

Table: 1127P

<table>
<thead>
<tr>
<th>Factors Associated with PFS</th>
<th>No. of Pts</th>
<th>Median PFS (weeks)</th>
<th>Univariate P-Value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Mets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57</td>
<td>24</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>12</td>
<td>0.01</td>
<td>2.73</td>
<td>1.20 – 6.20</td>
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</table>

Purpose: Ipilimumab was the first agent approved for the treatment of unresectable or metastatic melanoma that showed an overall survival benefit in a randomised phase III trial. Here, we evaluate the safety and efficacy of ipilimumab treatment outside of clinical trials in patients enrolled in the EAP in Italy.

Methods: Ipilimumab was available upon physician request for patients aged ≥16 years with unresectable stage III/IV melanoma who 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 monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each ipilimumab dose using Common Terminology Criteria for Adverse Events v3.0.

Results: In total, 848 Italian patients participated in the EAP from June 2010 to April 2012 across 53 centres. Of these 848 patients, data are currently available for 563 patients. With a median follow-up of 3 months, the disease control rate among 408 evaluable patients was 31.4%, including 7 patients with a complete response, 51 with a partial response and 89 with stable disease. As of April 2012, median progression-free survival and overall survival were 3.1 months and 6.2 months, respectively, with a 1-year survival rate of 34%. In total, 51.1% patients reported an AE of any grade, most of which were drug-related (36.2%). Grade 3/4 AEs were reported by 18.5% patients and considered drug-related in 8.5%. Eleven patients discontinued treatment due to toxicity. AEs were generally reversible with treatment as per protocol-specific guidelines. Complete data on all 848 patients, with longer follow-up, will be presented.

Conclusions: Ipilimumab is a feasible treatment option for pretreated patients who progressed on, or were unable to tolerate previous therapies. Many patients experienced durable disease control.

Disclosure: P.A. Ascerto: PA has served as a consultant for Merck Sharp & Dohme, as an advisor to Bristol-Meyers Squibb (BMS), Merck Sharp & Dohme, Roche, GlaxoSmithKline, Amgen, Celgene, Medimmune and Novartis. He has received honoraria from BMS, Merck Sharp & Dohme and Roche. Viera Chiarion Sileni: Vania Chiarion Sileni has acted as an advisor for Bristol-Myers Squibb, Roche.
that treatment with IPI was generally tolerable for pts in select subgroups. **Not mutually exclusive; †Off treatment before re-induction; ‡Terminated in US after FDA approval of IPI; ‡‡70 days of last induction dose**.

### Background
Treatment protocol CA184-045, a component of the EAP, provides a large safety database for IPI. Study 045 included pts with disease characteristics typically excluded from registration clinical trials such as ECOG PS of 2, asymptomatic brain metastases (BM) and primary ocular (OM) and mucosal (MM) melanoma. We now report safety data by subgroups for pts treated in the US at 3 mg/kg from March 2010 through July 2011.

### Methods
Eligible pts who had unselectable Stage III or IV melanoma that progressed on at least one systemic therapy and had no alternative treatment options. Treatment algorithms were used for identification and management of immune-related adverse events (AEs). During induction, pts received 3 mg/kg IPI iv q 3 wks up to 4 doses. All AEs and on-study deaths were collected. This analysis includes events through 70 days post last induction dose.

### Results
2017 pts were included in this analysis; 96% were Stage IV and 92% were 

### Table: 1129P

<table>
<thead>
<tr>
<th>Demographics, % Males ≤ 65 yrs Received all 4 induction doses</th>
<th>Age Group</th>
<th>Melanoma Sub-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N = 2017</td>
<td>≤ 65 yrs n = 1250</td>
<td>≥ 65 yrs n = 767</td>
</tr>
<tr>
<td>Demographics, % Males ≤ 65 yrs Received all 4 induction doses</td>
<td>64 62 59</td>
<td>61 – 58</td>
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<tr>
<td>Discontinuations, % Disease progression</td>
<td>93 49 42</td>
<td>92 52 31</td>
</tr>
<tr>
<td>Study drug toxicity Adverse event</td>
<td>21 17</td>
<td>20 16</td>
</tr>
<tr>
<td>Study terminated: Other</td>
<td>22 16</td>
<td>16 15</td>
</tr>
<tr>
<td>Select Grade 3/4 drug-related AEs, %</td>
<td>3 3 0.3 &lt;0.1</td>
<td>3 2 0.2 0.2</td>
</tr>
<tr>
<td>Diarrhea Colitis Gl Perforations</td>
<td>0.1 0.5 0.5</td>
<td>0.2 0.4</td>
</tr>
<tr>
<td>Hepatitis Brain edema Pruritus Rash</td>
<td>0.1 0.8</td>
<td>0.6 0.9</td>
</tr>
<tr>
<td>Death†, % Disease study toxicity</td>
<td>31 28 0.2</td>
<td>32 29 0.3</td>
</tr>
</tbody>
</table>

### Purpose
Mucosal melanoma is an extremely rare and aggressive malignancy associated with a poor prognosis. Because of its rarity and the challenges associated with each anatomical location, mucosal melanoma often remains undetected until it is at an advanced stage, when effective treatment options are limited. The EAP provided an opportunity to assess the activity and safety of ipilimumab in patients with mucosal melanoma outside of controlled clinical trials from the EAP in Italy.

### Methods
Ipiilimumab was available upon physician request for patients aged ≥16 years with stage III (unselectable) or stage IV skin, ocular or mucosal melanoma, who had failed or did not tolerate previous treatments and for whom no therapeutic option was available. Patients were treated with ipilimumab 3 mg/kg 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 monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each scheduled visit using Common Terminology Criteria for Adverse Events v3.0.

### Results
Of 848 Italian patients participating in the EAP, 70 (8.2%) had mucosal melanoma. Of these, data are available for 50 patients. With a median follow-up of 2.5 months, the disease control rate among 39 evaluable patients was 23.1%, including one patient with a complete response, two patients with a partial response and six with stable disease. As of April 2012, median progression-free survival and overall survival among patients with mucosal melanoma were 3.9 months and 6.2 months, respectively. In total, 40.0% patients reported an AE of any grade, most of which were drug-related (32.0%). Grade 3/4 AEs were reported by 18.0% patients and considered drug-related in 12.0%. AEs were generally manageable and most resolved with treatment as per protocol-specific guidelines.

### Conclusions
Results from the EAP suggest that ipilimumab is active in some patients with mucosal melanoma and warrants further investigation in prospective clinical trials.

### Disclosure
E. Simeone: Ester Simeone has received honoraria from Bristol-Myers Squibb. V. Chiariot Sileni: Vanna Chiaron Sileni has acted as an advisor for Bristol-Myers Squibb, Roche, GlaxoSmithKline, Merck Sharp & Dohme and Schering-Plough.

### Acknowledgments
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Efficacy and Safety of Ipilimumab Reinduction Therapy Patients with Pretreated Advanced Melanoma: Participating in an Expanded Access Programme (EAP) in Italy

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Purpose: In the registrational phase III trial of ipilimumab, patients who progressed after initially responding to ipilimumab treatment could subsequently receive additional ipilimumab therapy with the same treatment regimen (reinduction). Here, we describe efficacy and safety data from the Italian subgroup of patients in the EAP who received reinduction with ipilimumab outside of a clinical trial setting.

Methods: Ipilimumab was available upon physician request for patients aged ≥16 years with life-threatening, unresectable stage III/IV melanoma who failed or did not tolerate previous treatments and for whom no therapeutic option was available. Induction therapy with ipilimumab was 3 mg/kg every 3 weeks for 4 doses. Patients who progressed after stable disease (SD) lasting ≥3 months or an initial partial response (PR) or complete response (CR) were eligible for reinduction therapy at the same dose/schedule. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each ipilimumab dose using Common Terminology Criteria for Adverse Events v3.0.

Results: Of 848 patients participating in the EAP in Italy, 59 received reinduction therapy. After a median follow-up of 10 months, the disease control rate among 26 reinduced patients with data available was 100%; comprising nine patients with a PR and 17 with SD. Overall, two only reinduced patients died as a result of disease progression, after 11 and 13 months. As of April 2012, median overall survival for patients that received reinduction therapy had not yet been reached. In total, 57% patients reported grade 1/2 AEs. Grade 3/4 AEs were reported by 15% patients, but only considered drug-related in one patient. AEs were generally reversible with treatment as per protocol-specific guidelines.

Conclusions: Considering available data, reinduction with ipilimumab resulted in durable objective responses and/or stable disease. No new types of toxicities occurred during reinduction and most events were mild-to-moderate.

Disclosure: P.A. Asciento: PA has served as a consultant for Merck Sharp & Dohe, and as an advisor to Bristol-Myers Squibb (BMS). Merck Sharp & Dohe, Roche, GlaxoSmithKline, Amgen, Celgene, Medimmune and Novartis. He has received honoraria from BMS, Merck Sharp & Dohe and Roche. P. Queirolo: Paolo Queirolo has acted as an advisor for Roche, GlaxoSmithKline, Bristol-Myers Squibb and Schering-Plough and received honoraria from Bristol-Myers Squibb and Roche. E. Simone: Ester Simone has received honoraria from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

Efficacy and Safety of Ipilimumab in Patients with Pretreated, Ocular Melanoma: Experience from Italian Clinics Participating in the European Expanded Access Programme (EAP)

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Purpose: Ocular melanoma is a rare malignancy with an incidence of 5.3–10.9 cases per million per year (Papastefanou and Cohen; J Skin Cancer 2011). Currently, the treatment of metastatic ocular melanoma is limited by the lack of an effective systemic therapy. The EAP provided an opportunity to assess the activity and safety of ipilimumab in patients with ocular melanoma outside of a controlled clinical trial in patients from the EAP in Italy.

Methods: Ipilimumab was available upon physician request for patients aged ≥16 years with stage III (unresectable) or stage IV skin, ocular or mucosal melanoma, including those with asymptomatic brain metastases, who had either failed systemic therapy or were intolerant to ≥1 systemic treatment. Induction therapy with ipilimumab was 3 mg/kg 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 monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each scheduled visit using Common Terminology Criteria for Adverse Events v3.0.

Results: Of 848 Italian patients participating in the EAP, 83 (9.8%) had ocular melanoma. Of these 83 patients, 55 have data available. With a median follow-up of 3 months, the disease control rate among 46 evaluable patients was 34.8%, including 3 patients with a partial response and 13 with stable disease. As of April 2012, median progression-free survival and overall survival among patients with brain metastases were 2.5 months and 3.8 months, respectively. In total, 50.0% patients reported an AE of any grade, most of which were drug-related (40.5%). Grade 3/4 AEs were reported for ipilimumab.

Conclusions: Ipilimumab shows activity in patients with advanced melanoma metastatic to brain, with safety results consistent to what has been previously reported for ipilimumab.

Disclosure: P. Queirolo: Paolo Queirolo has acted as an advisor for Roche, GlaxoSmithKline, Bristol-Myers Squibb and Schering-Plough and received honoraria from Bristol-Myers Squibb and Roche. E. Simone: Ester Simone has received honoraria from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.
Advisor for Merck Sharp & Dohme, and as an advisor to Bristol-Myers Squibb (BMS), Roche, GlaxoSmithKline, Amgen, Celgene, Medimmune and Novartis. He has received honoraria from BMS, Merck Sharp & Dohme and Roche. All other authors have declared no conflicts of interest.

LONG-TERM SURVIVAL OF PATIENTS WITH ADVANCED MELANOMA TREATED SECOND LINE WITH IPILIMUMAB

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Objective: To estimate the long-term survival of patients with advanced melanoma treated second-line with ipilimumab 3mg/kg compared to no active treatment (best supportive care [BSC]).

Methods: At the end of the Phase III trial (MDX010-20) 17% of patients receiving ipilimumab were alive compared to 4% of those receiving GP100: median follow up 28 months, maximum 55 months. Trial data were used to model survival beyond the trial period. GP100 has been shown to have no impact on survival (within 28 months, maximum 55 months). Trial data were used to model survival of patients receiving BSC. Two groups were seen: Patients who experience therapy benefit and enter a stable period leading to a gradual plateau of model survival of patients receiving BSC. Those selected having an MAE of 0.003 (0.004 for long-term survivors) on the KM curve; Patients whose immune systems do not respond quickly and die causing an initial steep drop in the KM curve and standard modelling techniques did not fit the available data well and underestimated the durable response of immunotherapy. Around 18 months the mortality hazard was shown to change in the ipilimumab arm meaning that different methods were required to predict survival before and after this time. We estimated long-term survival as follows: <18 Months Kaplan-Meier data was used, mimicking survival within the trial · >18 Months · >5 years (representing the maximum data available from MDX-010-20) a standard parametric curve was fitted to the data · >5 years 15 year registry data from Balch et al (2001) for Stage IV melanoma and background mortality were used to estimate long-term survival.

Results: Using the three-part approach reduced the mean absolute error (MAE) associated with the curve fits. Those selected having an MAE of 0.003 (0.004 for long-term survivors) on the ipilimumab arm, and 0.008 (0.012 for long-term survivors) on the BSC arm. This compares to a MAE at least 7 x higher (0.06) for standard parametric curves. For BSC patients, the model predicts mean survival of 1.2 years whereas those taking ipilimumab are expected to survive for a mean of 3.7 years. This is due to more patients remaining alive beyond 5 years, after which death from melanoma is less likely.

Conclusion: Treatment with ipilimumab provides a substantial increase in survival over BSC in the second-line treatment of advanced melanoma.

Disclosure: D. Lee: Funding for the analysis conducted was provided to BresMed by BMS. I have not received any personal funding and do not have any personal interest in BMS or any competitor products. L. Pericleous: I have worked for BMS. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products. M. Lebmeier: I work for BMS. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products. B. Wim: Funding for the analysis conducted was provided to BresMed by BMS. I have not received any personal funding and do not have any personal interest in BMS or any competitor products. A. Batty: Funding for the analysis conducted was provided to BresMed by BMS. I have not received any personal funding and do not have any personal interest in BMS or any competitor products. T. Nikogliou: I work for BMS. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products.

SEQUENTIAL COMBINATION OF LOW DOSE CHEMO-MODULATING TEMOZOLOMIDE WITH FOTEMUSTINE IN METASTATIC MELANOMA (MM), A PHASE II STUDY

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Background and purpose: MM is a chemo-resistant cancer with poor prognosis. Further progress is likely to come from novel targeted antiBRAF therapy, available for about 50% of pts, and from immunotherapeutic agents such as the mAb ipilimumab, at present available only in some countries. Preclinical and clinical experiences support the concept that continuous exposure to an alkylating agent can effectively deplete cells of the DNA repair enzyme O6-methylguanine DNA methyltransferase, the primary mechanism of tumor resistance to chemotherapeutic agents like nitrosourea analogs. Our study was finalized to verify this hypothesis using a sequential combination of low dose chemo-modulating TMZ and FM. Primary endpoints were safety and tumor response evaluation.

Methods: 53 consecutive MM pts were enrolled in the study. The majority of them (80%) were enrolled before the targeted therapy. The main characteristics included: median age 56 years (21-79); ECOG PS 1 (0-2); number of disease sites: 1 in 30%, 2 in 27%, >2 in 43%; M status: M1a 9%, M1b 21%, M1c 70% with 5 pts having brain metastases. The following schedule was used: oral TMZ 100 mg/m2 d 1 and 2; FM iv 100 mg/m2 d 2, 4, 6, 8, and 10. The regimen was repeated every 3 weeks for a maximum total of 9 cycles. Tumour assessments were conducted at baseline and then every 3 cycles.

Results: 52 pts are evaluable for toxicity and 51 for clinical assessment (1 withdrew consent prior to starting treatment). Performance status was evaluated every 2 cycles. Disease cycles administered was 7 (range 2-9). There were 13 (25%) responses (1 CR and 9 PRs) with a median duration of 7 months, and 12 (23%) stable disease. Median progression-free survival was 6 months and median overall survival 11+ months (range 2-35+ months). Drug-related toxicities ≥ grade 3 included thrombocytopenia (10%), neutropenia (6%), anemia (2%), and hepatopathy (2%). Approximately 75% of pts were treated without dose reduction. Two patients (4%) discontinued therapy due to toxicities.

Conclusions: sequential low dose TMZ and FM demonstrated a high activity in our patient population with an acceptable toxicity. This schedule could therefore represent a good alternative for patients not eligible for targeted therapy or in whom previous targeted therapies failed. The study of the correlation between MGMT level and clinical outcomes is ongoing.

Disclosure: All authors have declared no conflicts of interest.
Annals of Oncology

1137P IMMUNO-CHEMOABLATION OF METASTATIC MELANOMA WITH INTRALESIONAL ROSE BENGAL

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Intralesional rose bengal (PV-10) is being investigated for treatment of solid tumors, where it may elicit selective chemoaulation of injected lesions and a tumor-specific, immune-mediated bystander response in untreated bystander lesions. In phase 1 testing in 20 subjects with AJCC Stage III-IV melanoma, single-dose treatment with PV-10 was well tolerated, producing a durable objective response (OR) rate of 12-24 weeks in 40% of subjects (20% CR + 20% PR by modified RECIST) and locoregional disease control (CR + PR + SD) in 75% of subjects; 15% of subjects achieved an OR in bystander lesions, which strongly correlated with response of their injected lesions. Phase 2 testing in 80 subjects with Stage III-IV metastatic melanoma (median age 70.0 yrs, range 33-97) commenced at 7 centers in Australia and the USA in October 2007, with final clinical evaluation completed in May 2010 (Clinical Trials ID NCTI00251053). In this study, subjects could receive up to four courses of PV-10 to treat 20 to 200 cutaneous lesions (median 2 courses, range 1-4). Preliminary study data was presented at SMR 2010 in Sydney, Australia, and showed that treatments were well tolerated, with adverse events predominantly mild to moderate, locoregional and transient, with no grade 4 or 5 AEs attributed to PV-10. Preliminary evaluation also showed robust response, with 24% of subjects achieving a CR, 25% PR and 22% SD of their target lesions. Additionally, 24% of 38 subjects with evaluable, untreated bystander lesions achieved CR in their bystander lesions, along with 13% PR and 18% SD. As observed in phase 1, response of bystander lesions strongly correlated with response of injected lesions. Finae efficacy and safety data will be presented, including response rate and time-to-event (progression free survival and overall survival). These data demonstrate that the safety and efficacy profile of PV-10 compares favorably with available and emerging treatment options for this patient population, and serve as the basis for phase 3 testing of PV-10 in Stage III patients with recurrent, in-transit or satellite metastases. A randomized controlled trial to assess PFS against standard care is expected to commence in the second half of 2012 at centers in Australia, the USA and the EU.


14 days intervals. Assessments were performed every 5 vaccine injections (10 wks) in DC-group and every 2 cycles (10 wks) in chemo group.

Results: From March 2010 to April 2012 101 patients were included in the study. After 2 cycles of chemo in 34 patients disease progression was detected. Of the 67 patients effects were not assessed in 3 patients. 31 patients were randomized to the DC-group and 33 to the chemo group. 6 pts were switched to chemo immediately after randomization and did not receive the vaccine. The 6-month PFS in per protocol population was 52.6% in the DC group and 15% in the chemo (BR = 0.56, 95% CI 0.34 to 0.97, p = 0.03). Median PFS was 7.38 mo in the DC group and 4.9 mo in the chemo group (95% CI 6.3 to 8.5 and 3.3 to 6.4, respectively, not significant). Median OS was 13.4 mo in the chemo group and was not reached in the DC group. Immunological testing suggested that population CD4 + CD25hiCD127+ (Treg) did not predict therapy success and did not significantly change during the treatment.

Conclusion: Dendritic cell vaccine immunotherapy may be a less toxic option for maintenance therapy in patients with metastatic melanoma with stable disease course. Additional trials are needed to compare such a vaccine with best supportive care or placebo.

Disclosure: All authors have declared no conflicts of interest.

1140P METASTATIC Uveal MELANOMA: A 22 YEARS SINGLE CENTER EXPERIENCE

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Uveal melanoma (UM) is the most frequent eye cancer (annual incidence 0.5-0.7/100,000). 40% to 60% of patients develop metastases; of them, up to 95% experience liver involvement. Metastatic disease carries a poor prognosis and no standard therapy is established so far. We retrospectively reviewed the medical records of 127 consecutive patients (M/F=61/65) with metastatic UM treated at our institution from September 1990 to February 2012. We collected: gender, age, TNM stage, data and site of primary UM and metastases; LDH, alkaline phosphatase, ggt, transaminases; treatments and outcome. Mean age at diagnosis of primary UM was 56.4 years (median 59.8, 95% CI 53.7-59.1 years). Mean age at diagnosis of first metastasis was 58.8 years (median 62.4, 95% CI 58.1-61.5 years), with a mean disease-free interval (DFI) of 3.6 years (median 1.9, 95% CI 1.9-5.3 years).

Nineteen (78%) patients had liver metastases (LM), 28 (22%) had local or nodal involvement, 9 (7.1%) had lung metastases and 13 (10.2%) had other visceral metastases (CNS, kidney, spleen, adrenal gland, bone), 30 (23.6%) patients had multiple sites of disease. Lung metastases were more frequent in females (OR 9.17, 95% CI 1.11-75.96, p = 0.037). LDH and ggt levels at the first metastasis onset, were inversely correlated with survival (<p<0.05). Survival was significantly poorer in LM bearers (13% versus 55% 1 year survival, p<0.01). Longer DFI was a prognostic factor for not hepatic recurrence and better prognosis (logistic regression, OR 0.88, 95% CI 0.78-0.99, p<0.05). Age at diagnosis correlated with age at recurrence and with longer DFI (p<0.05). Considering all treatments, almost always combining locoregional and systemic therapy with fotemustine, [hepatic intra-arterial fotemustine], radiofrequency, alcoholization, surgery, intra-arterial hepatic chemoembolization with camptochein charged microspheres (TACE), only TACE was associated with an improved prognosis (OR 0.17, 95% CI 0.06-0.46, p<0.01) and with a longer survival after metastasis diagnosis (=p=0.02).

Conclusions: TACE can be combined with systemic therapy and provides a clinical benefit in UM metastases, this encourages further prospective studies, also in combination with antiangiogenic drugs and systemic therapies.

Disclosure: All authors have declared no conflicts of interest.

1141P PERCUTANEOUS HEPATIC PERFUSION (CHEMOSAT® OR CS-PHP) OF MELPHALAN VS. BEST ALTERNATIVE CARE (BAC) IN PATIENTS (PTS) WITH HEPATIC METASTASES FROM MELANOMA: UPDATE OF A RANDOMIZED PHASE 3 STUDY

H.P. Alexander, Jr., on behalf of Phase 3 Principal Investigators

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Background: CS-PHP (CHEMOSAT®; Delcath Systems Inc, New York, NY) is being investigated for treatment of solid tumors, where it may elicit selective chemoablation of injected lesions and a tumor-specific, immune-mediated bystander response in untreated bystander lesions. In phase 1 testing suggested that population CD4 + CD25hiCD127+ (Treg) did not predict therapy success and did not significantly change during the treatment.

Conclusion: Dendritic cell vaccine immunotherapy may be a less toxic option for maintenance therapy in patients with metastatic melanoma with stable disease course. Additional trials are needed to compare such a vaccine with best supportive care or placebo.

Disclosure: All authors have declared no conflicts of interest.
or cutaneous melanoma. A survival update was performed on 31 March 2011. CS-PHP melphalan 3.0 mg/kg ideal body weight was infused into the hepatic artery over 30 min with concurrent extracorporeal filtration for 60 min. Up to 6 treatments were given every 4-8 wks. In the BAC group, crossover to CS-PHP melphalan was permitted after hepatic disease progression. The primary endpoint was investigator-assessed hepatic progression-free survival (hPFS). An exploratory post-hoc analysis of pts who crossed from BAC to CS-PHP vs. BAC-only pts was also performed.

Results: 93 pts were randomized to CS-PHP (n = 44) or BAC (n = 49). After hepatic disease progression, 28 pts crossed over to CS-PHP. Results are shown in the Table. The most common grade 3/4 toxicities in CS-PHP pts (n = 40) were hematological peri-procedural thrombocytopenia (73%) and anemia (55%) and post-procedural (beyond day 4 post-treatment) neutropenia (93%) or thrombocytopenia (83%). The safety profile in crossover pts was similar to that in pts randomized to CS-PHP melphalan.

Conclusions: CS-PHP melphalan significantly prolonged hPFS compared with BAC in pts with liver-dominant metastatic melanoma, thereby meeting the primary study objective. Efficacy was similar after hepatic disease progression in BAC-CS-PHP crossover pts as in those randomized initially to CS-PHP.

Disclosure: All authors have declared no conflicts of interest.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Median hPFS, mo</th>
<th>Hazard ratio (95% CI)</th>
<th>Median OS, mo</th>
<th>Hazard ratio (95% CI)</th>
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<tr>
<td>CS-PHP</td>
<td>44</td>
<td>8.0</td>
<td>0.35 (0.23-0.54)</td>
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<tr>
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<td>49</td>
<td>8.6</td>
<td>F &lt; 0.001</td>
<td>9.9</td>
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<td>BAC only</td>
<td>21</td>
<td>1.6</td>
<td>0.32</td>
<td>4.1</td>
</tr>
<tr>
<td>BAC → CS-PHP</td>
<td>28</td>
<td>8.8</td>
<td>15.3</td>
<td></td>
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</tbody>
</table>

THE CONCORDANCE OF HER2 STATUS IN PRIMARY AND METASTATIC SITES OF EXTRAMAMMARY PAGET’S DISEASE

R. Tanaka1, Y. Sasajima2, H. Tsuda3, K. Namikawa1, A. Tsutsumida1, N. Yamazaki1
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Background: HER2-targeted therapies have been introduced to treat breast and stomach cancers that show HER2 protein overexpression and/or HER2 gene amplification. However, the HER2 status of primary tumors and their corresponding metastatic sites is shown to be heterogeneous in less than 20% of cases. In extramammary Paget’s disease (EMPD), HER2 protein overexpression and gene amplification has been shown to occur in 5-80% of cases; however, knowledge regarding the concordance of HER2 status in primary and metastatic sites of EMPD is limited. The aim of this study was to clarify the concordance rate of HER2 status in the primary tumors and metastatic sites of EMPD.

Methods: Twenty-six tissue blocks of primary tumors and corresponding lymph node metastases were subjected to an immunohistochemistry (IHC) analysis. The IHC scores were classified into four groups (0 to 3+) according to the American Society of Clinical Oncology/College of American Pathologists Guidelines (2007). When the primary tumors and lymph node metastases showed IHC scores of either 2+ or 3+, the presence of HER2 gene amplification was examined using fluorescence in situ hybridization (FISH) and dual-colored in situ hybridization (DISH).

Results: immunohistochemically, 27% (7/26) of the primary tumors and 38% (10/26) of the lymph node metastases showed IHC scores of either 2+ or 3+. When HER2 protein overexpression was classified as being either positive (2+ or 3+ or negative (0, 1+), the concordance rate of the HER2 status of the primary tumors and corresponding lymph node metastases was 85% (22/26). The presence of HER2 gene amplification was examined in six primary tumors and 10 metastatic sites. HER2 gene was amplified in a total of seven cases (27%): four cases in both the primary and metastatic sites, two cases in the metastatic sites only and one case in the primary site only.

Conclusion: Good concordance of HER2 protein overexpression and gene amplification status was seen in the primary tumors and corresponding lymph node metastases of patients with EMPD. Furthermore, the HER2 gene was found to be always amplified in cases with an IHC score of 3+ and in two cases with an IHC score of 2+ in the lymph node metastases, which is suitable to be targeted for therapy.

Disclosure: All authors have declared no conflicts of interest.

A COMPARISON OF GENERAL POPULATION AND PATIENT UTILITY VALUES FOR ADVANCED MELANOMA

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Background: Health-related quality of life (HRQL) is a fundamental part of health technology assessment. Utility values are vital because they can be used as preference weights and allow the calculation of HRQL benefits. The objective of this study was to compare utilities calculated for patients with advanced melanoma in the Phase III clinical trial for ipilimumab (MDX010-20) using a generic and a condition-specific preference-based measure to utilities produced by vignettes for advanced melanoma. A secondary objective was to determine how different analyses might be used most appropriately within cost-effectiveness modelling.

Methods: The trial utilities were generated using the condition-specific EORTC-8D (1,190 observations) and generic SF-6D (1,157 observations) preference-based measures. Progression-status and time-to-death analyses were conducted on the patient-level data and the predictive abilities were compared. Patient-level results were compared to the utilities derived for progression status using vignettes valued by the general population.

Results: On disease progression, vignette-generated utilities showed a greater decrease (0.77 to 0.59) than either the generic SF-6D (0.64 to 0.619) or condition-specific EORTC-8D (0.763). SF-6D and EORTC-8D showed a large decrease in utility in the 180 days prior to death (0.826 to 0.628 and from 0.655 to 0.505, respectively). Compared to progression status, time to death showed a lower Root Mean Squared Error and higher R2 when used to predict patient utility.

Conclusion: Practitioners should carefully analyse patient level utility data prior to constructing economic models as standard measures, such as progression status, may not fully capture the patient experience. Similarly, where vignettes are valued to represent health states in an economic model, their applicability to the disease and patient population should be carefully scrutinised. The use of standard progression-based cost-effectiveness modelling techniques may not be appropriate for this disease. Consequently, there are implications for the analysis of utility information in future studies and the methods of cost-effectiveness modelling used for cancer treatments.

Disclosure: A. Batty: BresMed were funded by BMS to conduct the analysis presented within this paper. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products. B. Wrin: BresMed were funded by BMS to conduct the analysis presented within this paper. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products. L. Pericleous: I have worked for BMS. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products. D. Lee: BresMed were funded by BMS to conduct the analysis presented within this paper. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products. T. Nikoglo: I work for BMS. Other than this I have not received any personal funding and do not have any personal interest in BMS or any competitor products. All other authors have declared no conflicts of interest.

CETUXIMAB IN METASTATIC SQUAMOUS CELL CANCER OF THE SKIN: A CASE SERIES

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Background: Treatment of metastatic squamous cell cancer of the skin (SCCS) is challenging. Only few therapeutic options including cisplatin-based combinations are currently available. In a recently published phase II trial, cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), has demonstrated a promising clinical activity with an overall 69% disease control rate (DCR) and 28% response rate (RR) in patients with unresectable SCCS. Whether this treatment is also effective in metastatic SCCS is unclear.

Treatment of metastatic squamous cell cancer of the skin (SCCS) is currently available. In a recently published phase II trial, cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), has demonstrated a promising clinical activity with an overall 69% disease control rate (DCR) and 28% response rate (RR) in patients with unresectable SCCS. Whether this treatment is also effective in metastatic SCCS is unclear.

Conclusion: To summarize the efficacy of cetuximab at any line in a series of patients treated for metastatic SCCS, we conducted a single-arm study of cetuximab as first-line therapy in patients with SCCS who had failed at least one prior chemotherapeutic regimen. The study was performed in four centres in Switzerland. We collected standard baseline data by reviewing the medical records of patients who had been treated with cetuximab at any line for metastatic SCCS.
patients’ records. Endpoints were DCR at 4-8 weeks, 12-14 weeks and 20-36 weeks of treatment. In addition, we evaluated the treatment-related toxicity.

Results: The median age of the patients was 67 years. A total of 10 cycles in median were applied (range 1-21). The DCR was 67% (4 of 6 patients) at 4-8 weeks, 50% (3 of 6 patients) at 12-14 weeks, and 33% (2 of 6 patients) at 20-26 weeks (Table 1). One patient showed a complete response (CR) after 4 weeks of treatment and is still in remission since then. Death due to sepsis occurred in one patient. 83% (5 of 6 patients) developed Grade I-III acne-like rash around week 3 of treatment. All patients who had their disease controlled at 4-8 weeks showed an acne-like rash (4 of 6 patients), 1 patient had a rash without disease control.

Conclusions: Cetuximab treatment in patients with metastatic SCCS achieved an overall DCR of 57% at 4-8 weeks of treatment. 1 of 6 patients had a CR. These data suggest that cetuximab may be effective in this setting.

Response and disease control rates.

<table>
<thead>
<tr>
<th>Response at</th>
<th>4-8 weeks</th>
<th>12-14 weeks</th>
<th>20-36 weeks</th>
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<tr>
<td>Variable</td>
<td>No</td>
<td>%</td>
<td>No</td>
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<tr>
<td>Complete response</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Partial response</td>
<td>3</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>67</td>
<td>50</td>
<td>33</td>
</tr>
</tbody>
</table>

Disclosure: All authors have declared no conflicts of interest.

1145 SENSITIVE DETECTION OF BRAF MUTATIONS USING MUTANT-ENRICHED PCR AND REVERSE-HYBRIDIZATION TESTSTRIPS

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Background: BRAF plays a key role in growth factor receptor induced signalling pathways. Somatic BRAF mutations are involved in oncogenesis and are found in various types of tumors, including colorectal, thyroid and skin cancer. Activating BRAF mutations confer resistance to anti-EGFR monoclonal antibody therapy. Moreover mutated BRAF is a prominent target of the drug vemurafenib.

Materials and methods: We have developed a reverse-hybridization StripAssay detecting nine BRAF mutations: c.1797T > C (V600A), c.1799_1800TG > AT (V600D), c.1799_1800TG > AA (V600E), c.1799_1800TG > GT (V600G), c.1798_1799G > AA (V600K), c.1798_1799G > G (V600L), c.1798_1799G > CG (V600Q) and c.1801A > G (V600E). The test is based on mutant-enriched PCR in the presence of a BRAF wild-type suppressor, followed by hybridization of PCR products to teststrips presenting a parallel array of allele-specific oligonucleotide probes. Bound sequences are visualized using streptavidin-alkaline phosphatase conjugate and colour substrates. The hybridization and detection steps can be carried out fully automated using commercially available instrumentation.

Results: Plasmid clones served as reference DNA templates to control for specificity. StripAssay performance was evaluated on genomic DNA obtained from cultured cell lines and formalin-fixed paraffin-embedded (FFPE) tissue. Using normal DNA spiked with serial dilutions of DNA from the BRAF-mutant tumor cell line HT29 or BRL1, the mutations c.1797T > A (V600E) and c.1798_1799G > TT (V600K) were shown to be detectable at a level of 1%.

Conclusions: The simultaneous detection of nine different mutations with high sensitivity will make the StripAssay a very useful tool for the assessment of the BRAF mutation status of cancer patients.

Disclosure: All authors have declared no conflicts of interest.

1146 INTER- AND INTRA- TUMOR HETEROGENEITY OF SOMATIC BRAF MUTATIONS IN MELANOMA

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7Oncology, GeneKo Sar, Athens, GREECE, 81st Department of Medical Oncology, Metropolitan Hospital, Athens, GREECE, 9Department of Mathematics, University of Athens, Athens, GREECE

Background: Somatic mutations of BRAF are correlated with improved outcomes in patients with Melanoma treated with the anti-BRAF tyrosine kinase inhibitor Vemurafenib (PLX4032). Heterogeneity of patient responses to Vemurafenib in patients pertaining to concordance between synchronous (intra-) tumors; between primary and metastasis; and within (inter-) tumor heterogeneity. Data extraction was conducted by two investigators. Predictive values of testing for the presence of BRAF (True positive) and ‘no detectable mutation’ (True negative) were assessed and 95% confidence intervals calculated. Positive and Negative Predictive Values are presented (PPV, NPV).

Results: Sixteen articles presented for synchronous, 13 for meta-synchronous, and 7 for retesting (intra-tumoral analysis). Data indicates that there is a significant level of concordance: a) between and within tumors. We conducted a systematic search of the literature to conducted by two investigators. Predictive values of testing for the presence of BRAF (True positive) and ‘no detectable mutation’ (True negative) were assessed and 95% confidence intervals calculated. Positive and Negative Predictive Values are presented (PPV, NPV).

Conclusions: Repetitive data sets indicated heterogeneity of BRAF genotype status between synchronous, meta-synchronous tumors, and also at the intra-tumoral level. PPV and NPV were worryingly high and outside of acceptable limits. Approximately 30% of patients may have dis-concordance in their BRAF reporting status. No obvious technical errors were identified to explain these differences. Severe studies were not to bidirectional DNA sequencing may affect several cancer types, and this may impact on biomarker driven stratification. More data is eagerly awaited.

Disclosure: All authors have declared no conflicts of interest.

1147 BRAF MUTATIONS ARE FREQUENT IN MALIGNANT MELANOMA IN ISRAELI POPULATION AND PREDICT POOR RESPONSE TO BIOCHEMOTHERAPY

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Introduction: Malignant melanoma is a highly-aggressive form of skin cancer. Lesions developing in non-chronically sun-damaged skin are associated with frequent activating mutations in BRAF with substitution of valine for glutamic acid at position 600 (BRAFV600E). The prognostic significance of BRAF mutation in patients with metastatic melanoma (MM) treated with chemohiotherapy is uncertain.

Patients and methods: We studied the prognostic significance of BRAF mutation in 69 patients with MM treated with chemohiotherapy at the Soroka Medical Center, Beer Chemohiotherapy consisted of BCNU, DTIC, cisplatin, IL-2, alpha-interferon, GM-CSF, cetuximab, and tamoxifen. Samples were micro-dissected at the molecular lab, Hacarmel hospital, and subjected to high resolution melting analysis using primers flanking codon 600 in the BRAF gene. All abnormal high-resolution melting traces were subjected to bidirectional DNA sequencing.

Results: Mean age-55 years (range 25-80); Gender-male/female – 41/28; Ucreration – 30/54; Site of primary lesion: limbs/neck/trunk/retina/mucous membranes – 12/10/4/2/3; Depth: T1/T2/T3/T4/undetermined -3/8/24/16/4; Lymph node biopsy: 32/54; Lymph node involvement: none/micrometastases/metastases – 14/2/6/16. BRAF mutation – 42/69 (61%). BRAF mutation correlated with poor response to treatment (P = 0.056), but had no effect on disease-free interval (DFI). DFI was affected only by nodal stage (P = 0.026). In Cox multivariate analysis only male gender was associated with worse prognosis (P = 0.03), while BRAF mutation showed a trend towards worse prognosis (P = 0.169).

Conclusions: BRAF mutation in patients with MM treated with chemohiotherapy may predict poor response to treatment. Disclosure: All authors have declared no conflicts of interest.

1148 SAFETY AND EFFICACY OF IPILIMUMAB 10 MG/KG AMONG PATIENTS WITH ADVANCED MELANOMA FROM ITALY ENROLLED IN A EUROPEAN COMPASSIONATE USE PROGRAM

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Purpose: Clinical studies of ipilimumab have shown improved survival and durable tumoral responses across a spectrum of doses and schedules. Here, we evaluate the use of ipilimumab 10 mg/kg outside of clinical trials in a setting similar to daily practice.

Methods: Ipilimumab was available upon physician request for patients (pts) aged ≥16 years with unresectable stage III/IV melanoma who had either failed
systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Induction therapy with ipilimumab 10 mg/kg was given on Week (wk) 1, 4, 7 and 10 with tumour assessments conducted at baseline, wk 1, and at wk 12. After using modified World Health Organization criteria, Maintenance therapy with ipilimumab was available q 12 wks from wk 24 for pts with evidence of clinical benefit. Pts were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events v3.0.

Results: In total, 131 pts with metastasis, received ≥1 dose of ipilimumab and were eligible for analysis. Of these, 43 (31.8%) completed the induction phase and 26 (35.1%) received maintenance therapy (median of 2 cycles; range: 1–13). The disease control rate was 32%, including 3 pts (4%) with a complete response, 62 pts (47%) with a partial response, and 13 (19%) with stable disease. Metastatic, progression-free survival (PFS) and overall survival (OS) was 3 months (95% CI: 2.3–3.7) and 7 months (95% CI: 5.3–8.7), respectively. For pts with brain metastases, PFS and OS were 3 months (95% CI: 2.4–3.6) and 4 months (95% CI: 2.4–5.6). The 3-year survival rate was 16.6%, with 11 long survivors pts (>3 yrs). Overall, 45 pts (61%) reported an AE of any grade; most commonly pruritus and diarrhea. Eight grade 3/4 AEs were reported, including diarrhea (n = 2), pain (including epigastric; n = 3) and one case each of fever, increased liver enzymes and pancytopenia. Most AEs were manageable through adherence to protocol-specific guidelines.

Conclusions: Ipilimumab is a feasible treatment option for pts who progressed on, or were unable to tolerate previous therapies, with approximately one-third of pts achieving disease control and a long-term survival benefit.

Disclosure: M. Maio: Advisory board and honoraria from: BMS and Roche. P. Querolto: Paola Querolto served on Advisory Board of Bristol Myers Squibb–Roche-Genentech, GSK and received honoraria from Bristol Myers Squibb and Roche-Genentech. A. Testori: I have a consultant or advisory relationship to disclose ( BMS, GSK, AMGEN advisory boards); I have honoraria to disclose (from Roche-Genentech, GSK, MSD and received honoraria from Brystol Myers Squibb). P. Nathan: I have received compensation for advisory board and speakers panel from BMS. All other authors have declared no conflicts of interest.

11150 SPANISH MELANOMA MULTIDISCIPLINARY GROUP (GEM) EXPERIENCE WITH IPILIMUMAB (IPI) IN THE EXPANDED ACCESS PROGRAMME (EAP)

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Objective: Retrospective review of the IPI-EAP experience in Spain. Patients and methods: Demographics were provided by BMS. Response (R), survival (S) and toxicity (T) were collected from a questionnaire (Q) distributed by the GEM to EAP treating physicians. IPI dose was 3mg/kg q 3 w 4 x 4. Patients (pts) progressing after initial response were eligible for reinduction. Results: 355 EAP requests result in 288 treated pts. Median Age: 59y (24-83); Male: 57.6%; Stage: IA 28.8%, IB 22.6%, II 15.4%, III A 15.4%, III B 8.7%, IV 3.6%. The disease control rate was 32%, including 3 pts (4%) with a complete response, 11 (7.9%) with partial response, and 3 (2.1%) with stable disease. Median survival rate was 16.6%, with 11 long survivors pts (>3 yrs). Overall, 45 pts (61%) reported an AE of any grade; most commonly pruritus and diarrhea. Eight grade 3/4 AEs were reported, including diarrhea (n = 2), pain (including epigastric; n = 3) and one case each of fever, increased liver enzymes and pancytopenia. Most AEs were manageable through adherence to protocol-specific guidelines.

Conclusions: IPI is a feasible treatment option for pts who progressed on, or were unable to tolerate previous therapies, with approximately one-third of pts achieving disease control and a long-term survival benefit.

Disclosure: J. Larkin: I have received honoraria from BMS. P. Corrie: I have undertaken consultation work and advisory Boards for BMS. J. Nobes: I have been sponsored by BMS to attend conferences. E. Marshall: I have received previous honoraria for Advisory board for BMS. S. Kumar: I have served on the advisory board for BMS. R. Plummer: I have received honoraria for advisory boards to BMS. P. Nathan: I have received compensation for advisory board and speakers panel from BMS. All other authors have declared no conflicts of interest.
mg/kg, for 4 cycles. We have focused on patients aged 70 or more years with previously treated, advanced melanoma.

**Results:** Information on 30 patients is available. Median age was 75 years (70-81). 53.3% were males. Liver and CNS metastases were respectively present in 26.7% and 13.3% of the patients; 53.3% had 3 or more metastatic sites, and 51.7% had elevated LDH. Performance status (ECOG) was 0-1 in 93.3%. Up to 26.7% of the patients had received previous adjuvant treatment, which consisted of high dose interferon in 75%. All patients had received previous first line chemotherapy, including 26.7% with 2 or more lines. Medium time from the diagnosis of metastatic disease to the first dose of IPI was 14.2 months. A total of 76.7% of the patients completed the 4 intended doses of IPI. Main reasons for early discontinuation were death or progression in all patients, with no patient discontinuing due to toxicity. Responses were evaluable in 26 patients: PR: 6 (20%) – including 3 (10%) with a delayed PR after an initial PD; SD: 3 (10%), and PD: 17 (56.7%). Out of the 4 non-evaluable patients, 3 had just completed treatment and 1 was still on therapy at the time of the data collection. So far, reinduction treatment has not been offered to any patient. Estimated median survival (Kaplan-Meier) is 180 days (5.9 months) (95% CI 119.7-240.2). One year survival rate is 21%. Prognostic factors of survival at baseline were peripheral blood lymphocytes > 1000 /ml (p = 0.005) and LDH > 1.5 X ULN (p = 0.027). The reported toxicity per patient has been mild: skin: 23.3% grade I and 13.3% grade II; liver 6.7% grade I; and diarrhoea 6.7% grade I, 3.3% grade III-IV. Only 4 patients experienced toxicity grade III to IV.  

**Conclusions:** Ipilimumab efficacy in older patients, when it is used outside a clinical trial setting, is in line to published phase III data. There is no increase in toxicity, making this treatment a valid option for older patients with previously treated metastatic melanoma.

**Disclosure:** J.A. Lopez Martin: Participation in Advisory Boards of BMS and speaker in educational activities of BMS. A. Berrocal: Participation in Advisory Boards and speaker in educational activities sponsored by BMS. All other authors have declared no conflicts of interest.

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**IPI-LIMUAMB TREATMENT AFTER ELECTROCHEMOTHERAPY COULD BE AN EFFECTIVE SEQUENTIAL COMBINATION APPROACH**

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**Background:** Electrochemotherapy (ECT) has shown to be effective as local treatment of disseminated superficial melanoma, but there is a lack of evidence of its potential systemic effect. Potential immunologic changes due to ECT could have an impact on the outcome of patients with metastatic melanoma. Potential immunologic changes due to ECT could have an impact on treatment of disseminated superficial melanoma, but this hasn’t been demonstrated yet. Combining ECT with new drugs, like ipilimumab (ipi), could be a new therapeutic strategy. T-regulatory cells (T-Reg) are immunosuppressive lymphocytes whose role during ipi therapy has still to be clarified. Our previous experience showed a reduction of T-Reg cells in patients responder to ipi.

**Patients and methods:** 20 patients with advanced melanoma (8 at stage IIIC and 12 IV M1c) underwent ECT with bleomycin. 5 patients were treated with ECT and no further therapies, while 15 pts were treated with ECT first and then, after progression, with ipi at 3 mg/kg for 4 cycles. We collected PBMC of these patients. Blood draw was performed at ECT day 0-1-15-30 and during follow-up, while during ipi therapy, at each cycle (week 4-7-10) and at every tumor evaluation (every 12 weeks).

**Results:** 5/20 (25%) patients, all at stage IIIC, had performed only ECT and showed a good local response (2 CR and 3 PR). No variation of T-Reg was detected after ECT treatment with median value of 0.40 % (range 0.40-2.6 %). 15/20 (75%) patients had a local response and developed visceral progression after ECT without significant reduction of T-Reg levels. The median T-reg value was of 0.7 (range 0.50-2.6%). During ipi treatment, we found a decrease of T-Reg of 0.10% per cycle. This result was consistent with our previous evidence in patients treated with ipi in Italian EAP. Moreover, 3/15 patients (20%) showed local CR and 2 of them also systemic PR lasting at 12.1 months of follow-up, with a median T-Reg value of 0.10%. 8/15 (53%) had both local and systemic SD with a median TTP of 7.9 months and a median T-Reg of 0.60%. 4/15 (27%) developed a local and distant progression and we found a small decrease with median T-Reg of 1.8%.  

**Conclusion:** ECT followed by ipi in patients with metastatic melanoma, may be more effective than ECT and ipi alone. This combination may represent a new option. Anyway, further studies are necessary to verify these data.  

**Disclosure:** All authors have declared no conflicts of interest.

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**PACLITAXEL/CARBOPlatin CHEMOTHERAPY AS SALVAGE TREATMENT IN METASTATIC MELANOMA: IS NON-CUTANEOUS MELANOMA DIFFERENT?**

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**Background:** There is limited data on salvage chemotherapy for metastatic, non-cutaneous melanoma after failure to dacarbazine-based chemotherapy. Given the high incidence of non-cutaneous melanoma in Korea, we focused on the treatment outcome of paclitaxel/carboplatin as salvage chemotherapy in noncutaneous metastatic melanoma.  

**Patients and methods:** We retrospectively analyzed patients with metastatic melanoma who underwent paclitaxel and carboplatin (PC) chemotherapy as salvage treatment at Samsung Medical Center (SMC) between February 2009 and February 2012. The treatment schedule is as follows: intravenous paclitaxel 175 mg/m² plus intravenous carboplatin at area under curve 5 (AUC 5) on day 1 of a 21-day interval. Overall response rate, overall and progression free survival were calculated.

**Results:** Thirty two patients (median age: 54 years, range 24 – 72 years) were treated with PC as salvage chemotherapy. All patients were pretreated and had previously received a median of 2 systemic therapies. With respect to primary site, 10 patients (31.3%) had cutaneous melanoma, 8 (25%) had acral melanoma, 10 (31.3%) had mucosal melanoma, 2 (6.3%) had ocular melanoma. Of 32 patients, 7 patients achieved partial response (PR) (21.9%) and 11 patients were stable disease (34.4%). Median progression free survival (PFS) was 2.53 months for all patients. PFS was 4.3 months for patients controlled disease (partial response and stable disease) compared to 1.37 months for patients with progressive disease (p = 0.0001). Median overall survival was 5.2 months without a significant difference between noncutaneous and cutaneous metastatic melanoma group (p = 0.75).

**Conclusion:** PC chemotherapy seems to be a reasonable therapeutic option in heavily pretreated metastatic melanoma patients. Especially, this combination chemotherapy appears to have definite and clinically meaningful activity when used as salvage therapy in metastatic melanoma including non-cutaneous melanoma.  

**Disclosure:** All authors have declared no conflicts of interest.

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**OUTCOME OF PACLITAXEL/CARBOPLATIN AS SALVAGE CHEMOTHERAPY IN NON-CUTANEOUS MELANOMA DIFFERENT?**

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