**10000** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

# Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: New recurrence-free survival results from the EORTC 1325-MG/Keynote 054 double-blinded phase III trial at three-year median follow-up.

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**Background:** We conducted the phase 3 double-blind EORTC 1325/KEYNOTE-054 trial to evaluate pembrolizumab vs placebo in patients (pts) with resected high-risk stage III melanoma. Based on 351 recurrence-free survival **(**RFS) events and at a median follow-up of 1.25 years (yrs), pembrolizumab improved RFS (hazard ratio (HR) 0.57, P<0.0001) as compared to placebo (Eggermont, NEJM 2018). This led to the approval of pembrolizumab adjuvant treatment by EMA and FDA. **Methods:** Eligible pts included those ≥18 yrs of age with complete resection of cutaneous melanoma metastatic to lymph node(s), classified as AJCC-7 stage IIIA (at least one lymph node metastasis >1 mm), IIIB or IIIC (without in-transit metastasis). A total of 1019 pts were randomized (stratification by stage and region) to pembrolizumab at a flat dose of 200 mg (N=514) or placebo (N=505) every 3 weeks for a total of 18 doses (~1 year) or until disease recurrence or unacceptable toxicity. The 2 co-primary endpoints were RFS in the intention-to-treat overall population and in pts with PD-L1-positive tumors. Here, we report an updated RFS analysis based on a longer follow-up. **Results:** Overall, 15%/46%/39% of pts had stage IIIA/IIIB/IIIC. At 3.05-yr median follow-up, pembrolizumab (190 RFS events) compared with placebo (283 RFS events) prolonged RFS, in the overall population and in the PD-L1 positive tumor subgroup (see Table). RFS was consistently prolonged across subgroups, in particular according to AJCC-7 staging, BRAF-V600 E/K mutation status. **Conclusions:** Pembrolizumab, administered at 200 mg every 3 weeks for up to 1 year as adjuvant therapy, provided, at a 3-yr median follow-up, a sustained improvement in RFS, which was clinically meaningful, in resected high-risk stage III melanoma. This improvement was consistent across subgroups. In the overall population, the 3-yr cumulative incidence of distant metastasis being the first recurrence was 22.3% (pembrolizumab group) vs 37.3% (placebo group) (HR 0.55, 95% CI 0.44-0.69). Clinical trial information: NCT02362594. Research Sponsor: Merck.

| | | 3-yr RFS rate | | Stratified by stage at randomization | |
|---|---|---|---|---|---|
| | N pts | Pembrolizumab | Placebo | HR | CI (HR)* |
| **Overall population** | 1019 | 64% | 44% | 0.56 | 0.47-0.68 |
| **PD-L1 positive** | 853 | 65% | 46% | 0.57 | 0.43-0.74 |
| **PD-L1 negative** | 116 | 57% | 33% | 0.45 | 0.23-0.90 |
| **Stage IIIA** | 152 | 81% | 66% | 0.50 | 0.22-1.16 |
| **Stage IIIB** | 472 | 66% | 47% | 0.56 | 0.39-0.81 |
| **Stage IIIC** | 395 | 54% | 32% | 0.57 | 0.40-0.81 |
| **BRAF-mutated** | 440 | 62% | 37% | 0.51 | 0.36-0.73 |
| **BRAF-WT** | 448 | 62% | 47% | 0.66 | 0.46-0.95 |

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**10001** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

## Long-term benefit of adjuvant dabrafenib + trametinib (D+T) in patients (pts) with resected stage III *BRAF* V600–mutant melanoma: Five-year analysis of COMBI-AD.

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**Background:** Previous results of the COMBI-AD trial (NCT01682083) showed a significant relapse-free survival (RFS) benefit with 12 mo of adjuvant D+T vs placebo (PBO) in pts with high-risk resected stage III *BRAF* V600E/K–mutant melanoma. In the primary analysis, 3-year RFS rates with D+T vs PBO were 58% vs 39% (hazard ratio [HR], 0.47 [95% CI, 0.39-0.58]; $P < .001$). An interim analysis of overall survival (OS) yielded 3-year OS rates of 86% with D+T vs 77% with PBO (HR, 0.57 [95% CI, 0.42-0.79]). Here we report data from 5-year analyses including long-term RFS and an updated cure rate model. **Methods:** COMBI-AD is a randomized, Phase III trial evaluating 12 mo of adjuvant D 150 mg twice daily + T 2 mg once daily vs 2 matched PBOs in pts with resected stage III *BRAF* V600E/K–mutant melanoma. Pts were stratified by *BRAF* status and disease stage (per AJCC 7 criteria). The primary endpoint is RFS; secondary endpoints include OS and distant metastasis–free survival (DMFS). A Weibull mixture cure rate model was applied to estimate the fraction of pts who will remain relapse free in the long term. As all patients had completed treatment by the time of the primary analysis, updated safety analyses were not performed. **Results:** This analysis represents a median follow-up of 60 mo for the D+T arm and 59 mo for the PBO arm. As of the data cutoff (Nov 8, 2019), 190 of 438 pts in the D+T arm and 262 of 432 pts in the PBO arm had an RFS event. Median RFS was not reached (NR; 95% CI, 47.9 mo-NR) with D+T vs 16.6 mo (95% CI, 12.7-22.1 mo) with PBO (HR, 0.51 [95% CI, 0.42-0.61]). The 4- and 5-year RFS rates were 55% (95% CI, 50%-60%) and 52% (95% CI, 48%-58%) with D+T vs 38% (95% CI, 34%-43%) and 36% (95% CI, 32%-41%) with PBO. These findings match those estimated by the cure rate model. The RFS benefit with D+T was evident across all AJCC 7 substages (HR [95% CI]: IIIA, 0.61 [0.35-1.07]; IIIB, 0.50 [0.37-0.67]; IIIC, 0.48 [0.36-0.64]). Median DMFS was NR in either arm but favored D+T (HR, 0.55 [95% CI, 0.44-0.70]). OS was not updated at this data cutoff as the prespecified number of events for the final OS analysis had not yet occurred. **Conclusions:** This 5-year analysis confirms the long-term benefit of adjuvant D+T in pts with resected stage III *BRAF* V600E/K–mutant melanoma. Clinical trial information: NCT01682083. Research Sponsor: Novartis Pharmaceuticals Corporation.

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**10002** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

# First safety and efficacy results of PRADO: A phase II study of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma.

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**Background:** OpACIN-neo tested 3 dosing schemes of neoadjuvant (neoadj) IPI+NIVO and identified 2 cycles of IPI 1mg/kg + NIVO 3mg/kg (I1N3) as the most favorable with a pathologic (path) response rate (pRR) of 77% and 20% grade 3-4 irAEs. After 17.6 months median FU, 1/64 (2%) patients (pts) with path response vs 13/21 (62%) of the non-responders ( $>$ 50% viable tumor cells; pNR) had relapsed. We hypothesized that therapeutic lymph node dissection (TLND) could be omitted in pts achieving a complete or near-complete path response ($\leq$10% viable tumor cells; major path response, MPR) in the index node (largest LN metastasis: ILN), whereas additional adjuvant (adj) therapy might improve the outcome of pNR pts. **Methods:** PRADO is an extension cohort of the multi-center phase 2 OpACIN-neo study that aims to confirm the pRR and safety of neoadj I1N3 and to test response-driven subsequent therapy. Pts with RECIST 1.1 measurable clinical stage III melanoma were included to receive 2 cycles of neoadj I1N3 after marker placement in the ILN. ILN resection was planned at wk 6. Pts that achieved MPR in the ILN did not undergo TLND; pts with pPR ( $>$ 10 – $\leq$50% viable tumor cells) underwent TLND; and pts with pNR underwent TLND and received adj NIVO or targeted therapy (TT) for 52 wks +/- radiotherapy (RT). Primary endpoints were pRR in the ILN and 24-month RFS. Estimated toxicity rates at wk 12 were calculated using a Kaplan Meier based method. **Results:** Between Nov 16, 2018 and Jan 3, 2020, 99 of 114 screened pts were eligible and enrolled. So far, 86 pts had $\geq$12 wks FU. 70/99 pts achieved a path response in the ILN (pRR 71%, 95% CI 61% - 79%); 60 (61%) had MPR. TLND was omitted in 58 (97%) of the MPR pts. There were 28 non-responders; 7 developed distant metastasis before ILN resection. To date, 8 of the 21 pNR pts had adj NIVO, 7 had adj TT and 7 had adj RT. The estimated grade 3-4 irAE rate at wk 12 was 24%. Due to toxicity, 10 pts (10%) received only 1 cycle I1N3 and in 3 pts ILN resection was not performed: 2 of these pts underwent TLND at wk 9 and one pt was not evaluated for path response. At data cutoff, the surgery-related grade 1,2 and 3 AE rates were 29%, 10% and 0% in pts who underwent ILN resection only vs 21%, 30% and 9% in pts who underwent subsequent TLND (p = 0.004). At ASCO 2020 all pts will have reached $\geq$12 wks FU. **Conclusions:** Neoadj I1N3 treatment induced a high pRR with tolerable toxicity. TLND was omitted in a major subset of pts, reducing surgical morbidity. Longer FU is needed to report safety and RFS when TLND is omitted in MPR pts. Clinical trial information: NCT02977052. Research Sponsor: BMS.

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**10003** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

## A phase II study to evaluate the need for > two doses of nivolumab + ipilimumab combination (combo) immunotherapy.

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**Background:** Standard of care nivolumab (nivo) + ipilimumab (ipi) combo immunotherapy is given for 4 doses in patients (pts) with unresectable stage III/IV melanoma. Whether 4 doses are needed is questionable as retrospective data suggest pts treated with <4 doses of combo due to toxicity can have durable benefit. No prospective trials have evaluated the efficacy of intentionally giving <4 doses of combo in unresectable stage III/IV melanoma. **Methods:** In this phase 2, multicenter clinical trial (n=60), pts with unresectable stage III/IV melanoma received 2 doses of nivo (1mg/kg) + ipi (3mg/kg) followed by a CT scan at week 6. Pts with complete (CR) or partial responses (PR) by RECIST 1.1 or stable disease without an increase in total measurable tumor burden had protocol defined early favorable anti-tumor effect (FATE) and ceased combo, transitioning to maintenance nivo. Pts without FATE at week 6 received the standard third and fourth doses of combo followed by maintenance nivo. The primary endpoint was response rate by RECIST 1.1 at week 12. Secondary endpoints included additional efficacy assessments and safety. **Results:** 41 pts (68%) had FATE at week 6. The best overall response rates (CR + PR) by RECIST at week 12 or any time afterwards were 48% (95% CI: 35.2-61.6%) and 53% (95% CI: 40.0-66.3%), respectively. 18%, 58%, 12%, 10% had 1, 2, 3, 4 doses of combo, respectively. With a median follow-up of 11 months, any grade treatment-related toxicity occurred in 100% (57% grade 3-4) of pts. Three pts died due to treatment-related toxicity (2 myocarditis, 1 possible adrenal insufficiency). Among the 19 pts without FATE at week 6 and not selected to de-escalate combo after dose 2, no pts ultimately responded with ongoing combo dosing. **Conclusions:** The first 2 doses of nivo + ipi appear to drive combo's response efficacy and toxicity. Early radiographic imaging at week 6 may be able to identify pts who do not respond to combo dosing beyond dose 2. Randomized studies are planned to evaluate 1 dose of combo to see if efficacy is maintained with reduced toxicity. Clinical trial information: NCT03122522. Research Sponsor: Bristol Myers-Squibb.

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**10004** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

## Significant antitumor activity for low-dose ipilimumab (IPI) with pembrolizumab (PEMBRO) immediately following progression on PD1 Ab in melanoma (MEL) in a phase II trial.

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**Background:** Combination PD1 + CTLA4 antibodies (Abs) shows greater response rate (RR) versus PD1 Ab alone in MEL, but RR after initial PD1 Ab progression awaits robust investigation. CTLA4 Ab alone after PD1 Ab progression has a historical RR of 13%. We report final results of the first prospective clinical trial evaluating IPI 1mg/kg + PEMBRO immediately following progression on PD1 Ab (NCT02743819). **Methods:** Patients (pts) with advanced MEL, no prior CTLA4 Ab for metastatic disease, and who had progressed on PD1 Ab as immediately prior therapy (or non-CTLA4 Ab combination) were eligible. Pts received PEMBRO 200 mg + IPI 1 mg/kg Q3W for 4 doses, then PEMBRO alone for up to two years. The primary endpoint was RR by irRECIST. After 35 pts, the study met its primary endpoint with 10/22 evaluable pts achieving a response. The trial was expanded to enroll a total of 70 pts in open-label accrual to further describe the RR for this regimen in an exploratory fashion. The data analysis cutoff was January 30, 2020. **Results:** 67/70 accrued patients were evaluable for treatment response. Prior treatments included 60 on PD1 Ab alone and 10 on PD1 Ab-based combinations. Of these, 10 pts had progressed in the adjuvant setting. Median length of treatment on prior PD1 Ab was 4.8 months. Response assessments included 4 CR, 17 PR and 16 SD for a RR of 31% (21/67) in evaluable pts, and 30% (21/70) in all enrolled pts. 4 pts with a PR and 6 with SD had unconfirmed responses making the irRECIST response rate 25% (17/67) and 24% (17/70) among evaluable and enrolled pts, respectively. Median progression free survival (PFS) was 4.7 mo (95% CI: 2.8-8.3) and PFS at six months was 45% (95% CI: 33%-57%). 15/70 (21%) pts experienced $\geq$ grade 3-4 drug-related AEs, the most common being diarrhea, rash and transaminase elevation. PD-L1 positive vs negative status from historical tumor specimens did not associate with RR. **Conclusions:** This is the largest prospective study of IPI 1mg/kg + PEMBRO, demonstrating significant antitumor activity and tolerability in MEL post-PD1 Ab. Clinical trial information: NCT02743819. Research Sponsor: Merck via Investigator Sponsored Trial.

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**10005** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

## Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI+PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy.

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**Background:** PD1 induces long-term responses in approximately 30% of MM pts, however 2/3 are resistant (innate or acquired) and will require further treatment. A subset of these pts will benefit from IPI or IPI+PD1, but these pts are yet to be identified. We sought to determine; i) response rate (RR) and survival to IPI+/-PD1 after PD1 progression, and ii) clinical predictors of response and survival to IPI+/-PD1. **Methods:** MM pts resistant to PD1 and then treated with IPI+/-PD1 were studied. Demographics, disease characteristics and baseline blood parameters were examined. Univariate, multivariate and backward elimination technique analyses were performed to create predictive models of response and overall survival (OS). **Results:** Of 330 MM pts resistant to PD1 (median time to prog 2.9 months [0.5 – 42.3], 12% adjuvant, 88% metastatic; 70% innate, 30% acquired), 161 (49%) had subsequent IPI and 169 (51%) had IPI+PD1. Characteristics at start of IPI+/-PD1 were similar in IPI vs IPI+PD1 groups (stage M1D 27% vs 34%; elevated LDH 38% vs 40%), except IPI group had more ECOG $\geq$1 (60% vs 34%) and less BRAF mutation (mut) (21% vs 37%). Median follow-up from start of IPI+/-PD1 was 22.3 months (19.8 - 25.8); RR was 22%, higher in IPI+PD1 (31%) vs IPI (12%) ($p < 0.01$). PFS and OS at 1 year were 20% and 48%, respectively; better with IPI+PD1 (27%/57%) vs IPI (13%/38%) ($p < 0.01$). PD1 setting (adjuvant/metastatic) and response did not impact response to IPI+/-PD1. Most pts progressing on adjuvant PD1 had IPI+PD1 (88%) and RR was 33%. Neither the interval between PD1 and IPI+/-PD1 nor use of other drugs affected response to IPI+/-PD1. RR was similar in BRAF WT (23%) vs BRAF mut (RR 21%) pts. In BRAF WT pts, RR was higher with IPI+PD1 vs IPI (38% vs 9%, $p < 0.01$), while RR was similar with IPI (24%) or IPI+PD1 (19%) in BRAF mut pts. One third of BRAF mut pts had BRAF inhibitors (BRAFi) prior to IPI+/-PD1 and lower RR (13%) vs those without BRAFi (RR = 25%, $p > 0.05$). High grade ($\geq$G3) toxicity (tox) was similar with IPI+PD1 (30%) or IPI (34%, $p = 0.48$), and was not associated with response. Stage III/M1A/M1B, normal LDH and treatment with IPI+PD1 were the best predictors of response (AUC = 0.69). These factors, in addition to sex (male), ECOG PS = 0, BRAF mut, progressed/recurred $>$ 3 months on PD1, and absence of bone mets were the best predictors of longer OS (AUC = 0.74). **Conclusions:** In pts resistant to PD1, IPI+PD1 has higher RR, longer survival, yet similar high grade tox than IPI alone. Predictive models of response & survival will help select pts for IPI+/-PD1 after progressing on PD1. Research Sponsor: None.

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**10006** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

# Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies.

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**Background:** Treatment options are limited for patients with advanced melanoma who have progressed on checkpoint inhibitors and targeted therapies. Adoptive cell therapy using tumor-infiltrating lymphocytes (TIL) leverages and enhances the body's natural defense against cancer and has shown durable responses in heavily pretreated melanoma patients. **Methods:** C-144-01 is a global Phase 2 open-label, multicenter study of efficacy & safety of lifileucel in patients with unresectable metastatic melanoma who have progressed on checkpoint inhibitors and BRAF/MEK inhibitors, if $BRAF^{v600}$ mutant. We report on Cohort 2 (N = 66) patients who have received TIL. Tumors were resected at local institutions, processed in central GMP facilities for TIL production, manufactured, cryopreserved & shipped back to sites in a 22-day process. Therapy consisted of one week of lymphodepletion, a single lifileucel infusion, and up to 6 IL-2 doses. ORR was based on RECIST v1.1 by investigator assessment. Data cutoff was Feb 2, 2020. **Results:** Baseline characteristics: 3.3 mean prior therapies (anti-PD1 100%; anti-CTLA-4 80%; BRAF/MEK inhibitor 23%), high baseline tumor burden (106 mm mean target lesion sum of diameters), 44% liver/brain lesions, 40.9% LDH $>$ ULN. ORR by investigator was 36.4% (2 CR, 22 PR) and DCR was 80.3%. Mean time to response was 1.9 months (range: 1.3-5.6). After a median study follow-up of 17.0 months, median DOR (mDOR) was still not reached. Six responders have progressed, 2 have died and 2 started other anti-cancer therapy without progression. The adverse event profile was consistent with the underlying advanced disease and the lymphodepletion and IL-2 regimens. Additional follow-up data will be available for presentation. **Conclusions:** Lifileucel treatment results in a 36.4% ORR and mDOR was not reached at 17.0 months of median study follow up in a heavily pretreated metastatic melanoma patients with high baseline disease burden who progressed on multiple prior therapies, including anti-PD1 and BRAF/MEK inhibitors, if $BRAF^{v600}$ mutant. Clinical trial information: NCT02360579. Research Sponsor: Iovance Biotherapeutics, Inc.

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**10007** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

## Overall survival and biomarker analysis of a phase Ib combination study of toripalimab, a humanized IgG4 mAb against programmed death-1 (PD-1) with axitinib in patients with metastatic mucosal melanoma.

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**Background:** Metastatic mucosal melanoma responds poorly to PD-1 blockade therapy in comparison with cutaneous melanoma. Vascular endothelial growth factor (VEGF) is indicated to play an important immunosuppressive role in mucosal melanoma. Combination of VEGF inhibition with PD-1 blockade might provide therapeutic opportunities. Toripalimab was approved as a second-line treatment for metastasis melanoma in Dec 2018. This study is to evaluate the safety and clinical efficacy of toripalimab combined with axitinib for the treatment of metastatic mucosal melanoma. (Clinical trial ID: NCT03086174). **Methods:** Patients with metastatic melanoma receive 1 or 3 mg/kg toripalimab Q2W in combination with 5 mg axitinib BID until disease progression, unacceptable toxicity, or voluntary withdrawal. Clinical response is assessed every 8 weeks according to RECISTv1.1. Tumor PD-L1 expression, tumor mutational burden (TMB), and gene expression profile (GEP) will be evaluated for correlation with clinical response. **Results:** From April 2017 to April 2018, 33 patients were enrolled in the study. No DLT or treatment related death was observed. 97% patients experienced treatment related AE (TRAE) and 39.4% patients experienced Grade 3-4 TRAEs. Most common TRAEs include diarrhea, proteinuria, hand and foot syndrome and hypothyroidism. Only one patient discontinued treatment due to TRAE. Among 29 treatment naïve mucosal melanoma patients, 14 PR and 11 SD were observed for an ORR of 48.3% and a DCR of 86.2%. The median DOR was 13.7 months. The median PFS was 7.5 months and the median OS was 20.7 months. PD-L1 expression or TMB had no significant differences in responders versus non-responders. In contrast, GEP scores of eight selected immune-related and four angiogenesis-related genes showed strong correlation with clinical response, whereas previous published immune related signature or angiogenesis signature alone had no correlation. **Conclusions:** Toripalimab combined with axitinib is a promising treatment option for metastatic mucosal melanoma. GEP scores of selected immune-related and angiogenesis-related genes might predict the response to the combination. A randomized 3-arm Phase 2 trial has been initiated to compare toripalimab plus axitinib with toripalimab or axitinib alone. Clinical trial information: NCT03086174. Research Sponsor: Shanghai Junshi Bioscience Co., LTD.

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**10008** **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

## Single-center phase I/Ib study of concurrent intrathecal (IT) and intravenous (IV) nivolumab (N) for metastatic melanoma (MM) patients (pts) with leptomeningeal disease (LMD).

*Isabella Claudia Glitza, Suzanne Phillips, Courtney Brown, Cara L. Haymaker, Roland L. Bassett, J. Jack Lee, Michelle L. Rohlfs, Jessie Richard, Masood Iqbal, Ida John, Ian E. McCutcheon, Sherise D. Ferguson, Amy B. Heimberger, Barbara Jane O'Brien, Sudhakar Tummala, Nandita Guha-Thakurta, Matthew Debnam, Elizabeth M. Burton, Hussein Abdul-Hassan Tawbi, Michael A. Davies; The University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Neurosurgery, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX; University Of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** MM pts with LMD have a dismal prognosis, with a median overall survival (OS) < 3 months and no approved therapies. IT administration of interleukin-2 (IL2) achieves survival in ~15% of MM LMD pts, but at cost of severe toxicities. Given the favorable clinical activity and safety of systemic anti-PD1, we hypothesized that IT N administration is safe and can achieve clinical benefit in pts with LMD. **Methods:** The primary objectives of this first-in-human study (NCT03025256) were to determine the safety and the maximum tolerated dose (MTD) of IT N given with IV N in MM pts with LMD. Eligible pts had MM, ECOG PS < / = 2, and evidence of LMD by MRI and/or CSF cytology. Dexamethasone < / = 4mg/daily was allowed. For cycle 1, IT N is administered via intraventricular reservoir on day (D) 1; Blood and CSF is collected at multiple time points for translational research. For subsequent cycles (every 14 days), pts receive IT N on D1, followed by IV N 240 mg on D2. IT N doses evaluated were 5, 10, and 20 mg. Bayesian mTPI methodology was used to define the MTD. The study was recently amended to allow for concurrent BRAF/MEK inhibitor(i) treatment. **Results:** To date, 15 pts have been treated: two at 5, three at 10, and 10 at 20 mg IT N. Median age at LMD diagnosis was 41.8 (30.9-73.2) years; 6 pts are male. All pts had radiographic evidence of LMD and neurological symptoms; 8 pts had positive CSF cytology. 12 pts received prior therapies for their MM: anti-PD1 (n = 11), BRAFi/MEKi (n = 9), chemo (n = 2), IT IL2 (n = 4) other (n = 2). 11 pts had prior XRT, including whole brain RT (n = 7). 1 pt was treatment-naïve. The median numbers of IT N doses was 4 (1-42). No grade (Gr) 4-5 AEs were attributed to IT N or IV N; only 4 events (Gr 1, n = 2; Gr2, n = 2) were possibly related to the IT N. With a median follow-up of 18.7 weeks (1-83.3 wks), the median OS is 46.1 weeks (0.1-83.3). Clinical response data, translational research endpoints, including changes in CSF cytokines and cfDNA, will be reported. **Conclusions:** The trial demonstrates the feasibility of prospective clinical trials in MM patients with LMD. The combination of IT/ IV N was safe and well-tolerated, with no unexpected systemic or neurological toxicity. Final presentation will include results of LMD composite response assessment, comparative analysis of longitudinal CSF/blood samples to assess immunologic effects. Finally, the interim OS of the patients is encouraging, and supports further evaluation of IT administration of immunotherapy agents for pts with MM and LMD. Clinical trial information: NCT03025256. Research Sponsor: Bristol- Myers Squibb.

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**10009** **Clinical Science Symposium, Fri, 8:00 AM-9:30 AM**

## Integrative tumor and immune cell multi-omic analyses to predict melanoma response to immune checkpoint blockade.

*Valsamo Anagnostou, Daniel C. Bruhm, Noushin Niknafs, James R White, John-William Sidhom, Julie E. Stein, Hua-Ling Tsai, Hao Wang, Zineb Belcaid, Joseph Christopher Murray, Petra B. Ross-Macdonald, Megan Wind-Rotolo, Alexander S Baras, Janis M. Taube, Robert B. Scharpf, Catherine Grasso, Antoni Ribas, Drew M. Pardoll, Suzanne Louise Topalian, Victor E. Velculescu; Bloomberg~Kimmel Institute for Cancer Immunotherapy, Baltimore, MD; Johns Hopkins Medical Institutions, Baltimore, MD; Johns Hopkins School of Medicine, Baltimore, MD; Johns Hopkins Bloomberg/Kimmel Institute for Cancer Immunotherapy and Kimmel Cancer Center, Baltimore, MD; The Johns Hopkins Hospital, Baltimore, MD; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Johns Hopkins University SOM, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD; Bristol Myers Squibb R and D, Pennington, NJ; Bristol-Myers Squibb, Princeton, NJ; The Johns Hopkins Medical Institutions, Baltimore, MD; UCLA JCCC, Los Angeles, CA; UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA; The Sidney Kimmel Comprehensive Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD; Johns Hopkins Kimmel Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD*

**Background:** The complex crosstalk between tumor and immune cells during immune checkpoint blockade mandates the development of integrated models to interpret the antitumor immune response and predict clinical outcome. **Methods:** We performed comprehensive genomic, transcriptomic and T cell repertoire analyses on tumor biopsies from 64 patients with advanced melanoma receiving nivolumab +/- ipilimumab on CheckMate-038 (NCT01621490). Tumor biopsies were obtained at baseline and 2-4 weeks on therapy. Machine learning and Cox proportional hazards regression analyses were employed to integrate multi-omics features in predictive models of response, defined by RECISTv1.1 as complete and partial response, and survival (PFS and OS). **Results:** Responding patients had a higher tumor mutation burden (TMB) than non-responders. Expressed TMB more accurately predicted overall survival than genomic TMB (log rank p = 0.028 vs 0.078). High tumor aneuploidy was associated with worse prognosis especially for the patients in the nivolumab + ipilimumab group (log rank p = 0.01). TCR sequencing of paired tumors before and on-treatment revealed that responders had a significantly higher number of unique TCR clones at baseline and more clonotypic shifts on-treatment (p = 0.0018). Gene rearrangement analyses using transcriptome data identified a higher number of rearrangements involving immunoglobulin (Ig) genes in baseline tumors from responders. Deconvolution of transcriptomic data confirmed an enrichment in tumor associated B cells in baseline tumors of responders, suggesting that pre-existing B cell infiltration is a predictor of clinical outcome. Random forests were utilized to integrate Ig rearrangements, expressed TMB and tumor aneuploidy, into a predictive model of response that was superior to TMB (AUC = 0.89 and 0.65 respectively). Multivariate Cox proportional hazards analysis incorporating the same features was utilized to generate a risk score for each patient; those with high risk scores had a significantly shorter PFS compared to low risk patients (median PFS 1.45 months vs 29.01 months, log rank p = 3.4e-06, HR = 9.18, 95% CI: 3.14-26.85). **Conclusions:** Our findings highlight the multi-faceted interactions between the tumor and the immune system and the importance of pre-existing T and B cell immunity in driving clinical response and PFS after immune checkpoint blockade, laying the groundwork for integration of genomic and immune features into predictive models that may ultimately optimize therapeutic decisions. Research Sponsor: Bristol Myers Squibb.

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**10010** **Clinical Science Symposium, Fri, 8:00 AM-9:30 AM**

## Using machine learning to predict immunotherapy response in advanced melanoma.

*Paul Johannet, Nicolas Coudray, Douglas M. Donnelly, George Jour, Irineu Illa-Bochaca, Yuhe Xia, Douglas Buckner Johnson, Lee E Wheless, James Randall Patrinely, Anna C. Pavlick, Jeffrey S. Weber, Hua Zhong, Aristotelis Tsirigos, Iman Osman; NYU School of Medicine, New York, NY; New York University School of Medicine, New York, NY; The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY; NYU Langone Medical Center, New York, NY; NYU Langone, New York, NY; Vanderbilt University Medical Center, Nashville, TN; Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY; Department of Population Health, New York University School of Medicine, New York, NY; NYU School of Medicine Department of Pathology, New York, NY*

**Background:** Several predictors of response to checkpoint inhibitors show potential, but use pathological assays and/or molecular characterization, which limits their clinical utility outside of the academic setting. We aimed to develop a streamlined approach by leveraging information immediately available through standard care. Here, we present a computational method that integrates deep learning on histology specimens with clinicodemographic variables to predict treatment outcomes in advanced melanoma. **Methods:** We used hematoxylin and eosin (H&E) sections from 72 patients ($n$= 153 slides) from New York University (NYU) to build a Segmentation Classifier that distinguishes tumor, lymphocyte, and connective tissue. Using pre-treatment H&E slides from 121 NYU patients ($n$ =302 slides), we trained a Response Classifier to predict response by selectively analyzing tumor regions. We then developed a logistic regression classifier that combines neural network output with clinicodemographic variables. The classifiers were tested on an independent cohort of 32 patients from Vanderbilt University ($n$ =42 slides). Area under the curve (AUC) was calculated as a measure of prediction accuracy. **Results:** The Segmentation Classifier distinguished tumor, lymphocyte, and connective tissue with AUCs 0.886-0.984. For the Response Classifier, optimal learning conditions were identified through training on NYU patients and testing on Vanderbilt patients (AUCs 0.685 and 0.728, respectively). The fully trained Response Classifier performed with AUC 0.711 on Vanderbilt patients. The logistic regression model performed with enhanced prediction accuracy with AUC 0.803 on NYU patients and AUC 0.793 on Vanderbilt patients. **Conclusions:** Histology slides and patients' clinicodemographic characteristics are readily available through routine standard of care and have the potential to predict immunotherapy response. Our approach is time-efficient, reproducible, and requires minimal resource allocation, thus overcoming multiple common barriers to generalizability for contemporary biomarkers. Research Sponsor: SPORE P50 CA016087, MRA Established Investigator Award.

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**10011** **Clinical Science Symposium, Fri, 8:00 AM-9:30 AM**

## Autoantibodies as predictors for survival and immune-related adverse events in checkpoint inhibition therapy of metastasized melanoma.

*Jessica Cecile Hassel, Hans-Dieter Zucht, Joanna Mangana, Reinhard Dummer, Claudia Pföhler, Kilian Wistuba-Hamprecht, Benjamin Weide, Lara Elena Hakim-Meibodi, Friedegund Elke Meier, Carsten Schulz, Manuel Bräutigam, Petra Budde; Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; Oncimmune Germany GmbH, Dortmund, Germany; University Hospital Zürich, Zürich, Switzerland; Skin Cancer Center in the Department of Dermatology at University Hospital Zürich, Zürich, Switzerland; Department of Dermatology, Saarland University Medical Center, Homburg/Saar, Germany; University of Tübingen, Tübingen, Germany; Department of Dermatology, University Hospital Tübingen, Tübingen, Germany; Department of Dermatology and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany; Department of Dermatology, University Hospital Dresden, Dresden, Germany*

**Background:** Increasing evidence suggests that the B cell response in cancer patients is an important component of anti-tumour immunity. Autoantibodies targeting tumour and self-antigens may serve as biomarkers of anti-tumour and auto-immunity. As they can be measured in patient' sera, they have great potential as clinical routine biomarkers. The objective of this study was to explore if autoantibodies are associated with survival and immune related adverse events (irAE) in patients with metastatic melanoma under checkpoint inhitibor (CPI) therapy. **Methods:** Pre-treatment serum samples from 333 metastatic melanoma patients receiving CPI therapy at 5 European centers were retrospectively used to identify autoantibody signatures for survival and irAE. We designed a cancer immunotherapy antigen array comprising 832 autoimmune and tumour antigens as well as immune and cancer pathway proteins. Statistical tests were separately performed for patients treated with anti-CTLA4 (alone or in combination) and with anti-PD1 antibody monotherapy. Cox-regression analysis and univariate statistical tests were applied for biomarker discovery. Progression free and overall survival was measured from treatment initiation to tumor progression or death date. irAE were recorded including onset date and grade (CTC-AE). **Results:** For each therapy group we identified a set of autoantibody reactivities in untreated melanoma patients that were associated with the development of irAEs and/or survival. The identified autoantibodies target a diverse set of antigens comprising neoantigens (p53), cancer testis antigens (MAGEB4), paraneoplastic antigens (gephyrin), autoantigens (ribosomal proteins, Nor-90) and FGFR1. Autoantigens that correlated with irAE and survival were e.g. anti-MAGEB4 and anti-FGFR1. Elevated anti-MAGEB4 pre-treatment levels were associated with longer overall survival ($p = 0.002$, $HR = 0.77$) and the development of irAEs ($p = 0.002$, $HR = 1.27$) in ipilimumab +/- nivolumab treated patients. Higher pre-treatment anti-FGFR1 antibodies were associated with shorter survival ($p = 0.008$, $HR = 1.27$) and a lower a lower frequency of irAEs ($p = 0.04$, $HR = 0.69$) in these patients. **Conclusions:** We identified autoantibody targets suggesting a diverse B cell response to antigens expressed in tumours and those associated with autoimmunity. Depending on the specific antigen, the immune response towards those antigens may be associated with anti-tumour or pro-tumour responses. Research Sponsor: Oncimmune Germany GmbH.

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## 10012 Poster Discussion Session; Displayed in Poster Session (Board #361), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# Update on overall survival in COLUMBUS: A randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with *BRAF* V600-mutant melanoma.

*Helen Gogas, Paolo Antonio Ascierto, Keith Flaherty, Ana Arance, Mario Mandalà, Gabriella Liszkay, Claus Garbe, Dirk Schadendorf, Ivana Krajsova, Ralf Gutzmer, Jan Willem de Groot, Caroline Dutriaux, Carmen Loquai, Ashwin Gollerkeri, Michael D Pickard, Caroline Robert, Reinhard Dummer; First Department of Medicine, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; Fondazione IRCCS-Istituto Nazionale dei Tumori, Naples, Italy; Dana-Farber Cancer Institute/ Harvard Medical School/Massachusetts General Hospital, Boston, MA; Hospital Clínic de Barcelona, Barcelona, Spain; Papa Giovanni XXIII Hospital, Bergamo, Italy; Országos Onkológiai Intézet, Budapest, Hungary; Eberhard Karls University, Tübingen, Germany; Universitaetsklinikum Essen & German Cancer Consortium, Essen, Germany; University Hospital Prague, Praha, Czech Republic; Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany; Oncological Center Isala, Zwolle, Netherlands; U1035 INSERM, University of Bordeaux, Bordeaux, France; University Medical Center Mainz, Mainz, Germany; Pfizer Inc, Cambridge, MA; Pfizer Inc., Boulder, CO; Gustave Roussy and Paris-Saclay University, Villejuif, France; Skin Cancer Center in the Department of Dermatology at University Hospital Zürich, Zürich, Switzerland*

**Background:** Treatment of patients with *BRAF* V600–mutant melanoma includes BRAF/MEK-inhibitor combinations based on demonstrated benefits on progression-free survival (PFS) and overall survival (OS). To better understand the proportion of patients who derive long-lived benefit and their characteristics, we performed an updated analysis of OS and other endpoints from the COLUMBUS trial. **Methods:** In Part 1 of COLUMBUS, 577 patients with advanced/metastatic *BRAF* V600–mutant melanoma, untreated or progressed after first-line immunotherapy, were randomized 1:1:1 to ENCO 450 mg QD + BINI 45 mg BID (COMBO450) vs VEM 960 mg BID (VEM) or ENCO 300 mg QD (ENCO300). An updated analysis including PFS, OS, objective response rate (ORR), and safety was conducted after an additional 24 months' follow-up from the initial analysis. The study is ongoing. **Results:** At data cutoff (November 2019, as-is data), events had occurred in 65%, 59%, and 75% of patients in the COMBO450, ENCO300, and VEM treatment arms, respectively. Across arms, median follow-up for OS was 60.6 months (mo), with median OS of 33.6 mo (95% CI, 24.4–39.2) for COMBO450, 23.5 mo (95% CI, 19.6–33.6) for ENCO300, and 16.9 mo (95% CI, 14.0–24.5) for VEM. Compared to VEM, COMBO450 decreased the risk of death by 38% (HR, 0.62 [95% CI, 0.49–0.79]). Updated median PFS was COMBO450, 14.9 mo (95% CI, 11.0–20.2), ENCO300, 9.6 mo (95% CI, 7.4–14.8), and VEM, 7.3 mo (95% CI, 5.6–7.9). PFS was longer for COMBO450 vs VEM (HR, 0.52 [95% CI, 0.40–0.67]). A landmark analysis showed a higher rate of OS for COMBO450 at each year analyzed, with OS rates at 4 years of 39%, 37%, and 26% COMBO450, ENCO300, and VEM, respectively. Updated safety analysis confirmed the beneficial long-term tolerability of COMBO450. **Conclusions:** In the COLUMBUS trial, results for updated PFS and OS with COMBO450 continue to demonstrate long-term benefits in patients with *BRAF* V600–mutated melanoma. Clinical trial information: NCT01909453. Research Sponsor: Pfizer Inc.

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## 10013 Poster Discussion Session; Displayed in Poster Session (Board #362), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# Long-term survival from pembrolizumab (pembro) completion and pembro retreatment: Phase III KEYNOTE-006 in advanced melanoma.

*Georgina V. Long, Jacob Schachter, Ana Arance, Jean-Jacques Grob, Laurent Mortier, Adil Daud, Matteo S. Carlino, Antoni Ribas, Catriona M. McNeil, Michal Lotem, James M. G. Larkin, Paul Lorigan, Bart Neyns, Christian U. Blank, Teresa M. Petrella, Omid Hamid, Erin Jensen, Clemens Krepler, Scott J. Diede, Caroline Robert; Melanoma Institute Australia, The University of Sydney, Royal North Shore Hospital, Mater Hospital, Sydney, Australia; Sheba Medical Center, Tel HaShomer Hospital, Tel Aviv, Israel; Hospital Clinic de Barcelona, Barcelona, Spain; Aix Marseille University, Hôpital de la Timone, Marseille, France; Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France; UCSF, San Francisco, CA; Melanoma Institute Australia, University of Sydney, Blacktown Hospital, and Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, Australia; David Geffen School of Medicine at UCLA, Los Angeles, CA; University of Sydney and Chris O'Brien Lifehouse, Sydney, Australia; Sharett Institute of Oncology, Hadassah-Hebrew Medical Center, Jerusalem, Israel; Royal Marsden Hospital, London, United Kingdom; University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom; Universitair Ziekenhuis Brussel, Brussels, Belgium; Netherlands Cancer Institute, Amsterdam, Netherlands; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; The Angeles Clinic and Research Institute, Los Angeles, CA; Merck & Co., Inc., Kenilworth, NJ; Gustave Roussy and Paris-Sud University, Villejuif, France*

**Background:** 5-year follow-up of the phase 3 KEYNOTE-006 study (NCT01866319) showed pembro improved OS vs ipilimumab (ipi) in patients (pts) with advanced melanoma. 3-y OS rate from pembro completion for pts who completed 2 y of pembro was 93.8%. Results with 8 mo of additional follow-up are presented to inform clinical care. **Methods:** Eligible pts with ipi-naive advanced melanoma, ≤1 prior therapy for *BRAF*-mutant disease, and ECOG PS 0 or 1 were randomized to pembro 10 mg/kg Q2W or Q3W for ≤2 y or ipi 3 mg/kg Q3W for 4 doses. Pts discontinuing pembro with CR, PR, or SD after ≥94 weeks were considered pts with 2-y pembro. Pts who stopped pembro with SD, PR or CR could receive ≤12 mo of additional pembro (2nd course) upon disease progression if still eligible. ORR was assessed per immune-related response criteria by investigator review. OS was estimated using the Kaplan-Meier method. Pembro arm data were pooled. Post hoc ITT efficacy analyses are shown. **Results:** Median follow-up from randomization to data cutoff (Jul 31, 2019) was 66.7 mo in the pembro and 66.9 mo in the ipi arms. OS outcomes are shown in Table. For the 103 pts with 2-y pembro (30 CR, 63 PR, 10 SD), median follow-up from completion was 42.9 mo (95% CI, 39.9-46.3).Median DOR was not reached. 36-mo OS from pembro completion was 100% (95% CI, 100.0-100.0) for pts with CR, 94.8% (95% CI, 84.7-98.3) for pts with PR, and 66.7% (95% CI, 28.2-87.8) for pts with SD. 15 pts received 2nd-course pembro; BOR in 1st course was 6 CR, 6 PR, and 3 SD. Median time from end of 1st course to start of 2$^{nd}$course was 24.5 mo (range, 4.9-41.4). Median follow-up in pts who received 2nd-course pembro was 25.3 mo (range, 3.5-39.4). Median duration of 2nd-course pembro was 8.3 mo (range, 1.4-12.6). BOR on 2$^{nd}$course was 3 CR, 5 PR (ongoing responses, 7 pts), 3 SD (ongoing, 2 pts), and 2 PD (1 death); 2 pts pending. **Conclusions:** Pembro improves the long-term survival vs ipi in pts with advanced melanoma, with all pts who completed therapy in CR still alive at 5 years. Retreatment with pembro at progression in pts who stopped at SD or better can provide additional clinical benefit in a majority of pts. Clinical trial information: NCT01866319. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

| | Deaths (additional since last data cutoff Dec 3, 2019), n | Median OS (95% CI), mo | HR | 5-Y OS rate (95% CI), % |
|---|---|---|---|---|
| **Pembro (N = 556)** | 328 (4) | 32.7 (24.5-41.6) | 0.74 | 39.7 (35.5-43.8) |
| **Ipi (N = 278)** | 173 (1) | 15.9 (13.3-22.0) | – | 31.0 (25.3-36.9) |
| **1L pembro (n = 368)** | 203 (1) | 38.7 (27.3-50.8) | 0.72 | 43.3 (38.0-48.4) |
| **1L ipi (n = 181)** | 111 (1) | 17.1 (13.8-26.2) | – | 33.0 (25.8-40.3) |
| **2L pembro (n = 97)** | 125 (3) | 23.5 (16.8-34.2) | 0.78 | 32.3 (25.5-39.3) |
| **2L ipi (n = 187)** | 62 (0) | 13.6 (10.7-22.0) | – | 27.3 (18.3-37.0) |

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## 10014 Poster Discussion Session; Displayed in Poster Session (Board #363), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# The nature and management of acquired resistance to PD1-based therapy in melanoma.

*Adriana Hepner, Judith M. Versluis, Camille Lea Gerard, Lauren Julia Brown, Roslyn Wallace, Prachi Bhave, Yanina Jansen, Oliver Klein, Allison Betof Warner, Joanna Mangana, Victoria Atkinson, Serigne Lo, Georgina V. Long, Douglas Buckner Johnson, Jennifer Leigh McQuade, Paolo Antonio Ascierto, Lisa Zimmer, Celeste Lebbe, Christian U. Blank, Alexander M. Menzies; Melanoma Institute Australia, Sydney, Australia; Netherlands Cancer Institute, Amsterdam, Netherlands; Center of Personalized Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland; Weastmead Hospital, Sydney, Australia; Peter MacCallum Cancer Centre, Melbourne, Australia; Alfred Health, Melbourne, VIC, Australia; Department of Surgery, Universitair Ziekenhuis Brussel, Brussels, Belgium; Medical Oncology Unit, Austin Health, Heidelberg, Australia; Memorial Sloan Kettering Cancer Center, New York, NY; University Hospital Zürich, Zürich, Switzerland; University of Queensland, Brisbane, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Royal North Shore Hospital, Mater Hospital, Sydney, Australia; Vanderbilt University Medical Center, Nashville, TN; The University of Texas MD Anderson Cancer Center, Houston, TX; Fondazione IRCCS-Istituto Nazionale dei Tumori, Naples, Italy; Department of Dermatology, University Hospital, University Duisburg-Essen, Essen, Germany; APHP Dermatology and CIC, U976, Université de Paris, Hôpital Saint-Louis, Paris, France; Melanoma Institute Australia, University of Sydney, Royal North Shore Hospital, Sydney, Australia*

**Background:** Anti-PD1 therapy (PD1), either alone or in combination with anti-CTLA4, has high initial response rates, but 20% of patients (pts) with complete response (CR) and 60% with partial response (PR) experience disease progression by 5 years. The nature and best management of this acquired resistance (AR) remains unknown. **Methods:** Consecutive pts from 16 centers who achieved CR or PR to PD1-based therapy and who later progressed were examined. Demographics, disease characteristics, nature of progression and subsequent treatments were examined. **Results:** 300 pts were identified, median age was 64y, 133 (44%) BRAF mutant and 55 (18%) had target therapy (TT) prior to PD1-based therapy. 173 (58%) received PD1 alone, 114 (38%) PD1+CTLA4 and 13 (4%) PD1 + an investigational drug. 89 (30%) pts had CR, 210 (70%) pts had PR. Median time to AR was 12.6 mo (95% CI, 11.3, 14.2) and 142 (47%) progressed while still on drug. Most pts (N = 194, 65%) progressed in a single organ site, and in a solitary lesion (N = 154, 51%). 38 (25%) progressed in the brain only. AR was in new lesion in 136 (45%), existing lesions in 106 (35%), and both new and existing lesions in 58 (19%). For those with solitary lesion progression, 51 (33%) had local (L) treatment alone, 54 (35%) had local and systemic (L+ST), 46 (30%) had systemic therapy alone (ST) and 3 (2%) had no further treatment (BSC). If progression was non-solitary, 89 (61%) had ST, 33 (23%) L+ST, 17 (12%) L alone and 7 (5%) BSC. For those who received ST after AR, first ST (ST1) was PD1 alone in 130 (51%) [53, 41% continuation, 77, 59% reinduction], PD1+CTLA4 in 31 (12%), CTLA4 alone in 15 (6%), targeted therapy in 49 (19%) and investigational drugs in 29 (11%). Median follow-up from AR was 20 mo (95% CI 18-22). The ORR to ST1 was 46% for PD1 alone (56% continuation, 42% reinduction), 56% for PD1+ CTLA4, 0% for CTLA4 alone, 20% for investigational drugs and 67% for TT. Median OS from AR was 38 mo (95% CI, 34.6-NR). 2y-OS was 69% in those with solitary progression compared to 55% for the pts that had a non-solitary progression ($p < 0.001$). There was no difference in OS by ST1 class. Detailed analyses including nature and management of AR while on PD1 or after discontinuation will be presented, as will site-specific AR outcomes. **Conclusions:** Acquired resistance to PD1-based therapy in melanoma is usually oligometastatic, occurring approximately one year after PD1 start. Most pts with isolated progression have local therapy, and the most frequent subsequent systemic therapy is PD1-alone. Patients with AR can have meaningful survival, with median OS over 3 years from AR. Research Sponsor: None.

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**10015 Poster Discussion Session; Displayed in Poster Session (Board #364), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM**

## Twenty-four months RFS and updated toxicity data from OpACIN-neo: A study to identify the optimal dosing schedule of neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in stage III melanoma.

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**Background:** Early results of the OpACIN-neo study testing 3 different dosing schedules of neoadjuvant IPI + NIVO demonstrated that 2 cycles IPI 1mg/kg + NIVO 3mg/kg (IPI1NIVO3, arm B) was the most favorable schedule with 20% grade 3-4 immunotherapy-related adverse events (irAEs) and a pathologic response rate (pRR) of 77%. After a median follow-up (FU) of 8.3 months, none of the 64 patients (pts) with a pathologic (path) response ( $<$ 50% viable tumor cells) versus 9/21 (43%) without a path response had relapsed. Here, we present the updated 2-year RFS, EFS and long-term toxicity data. **Methods:** In the phase 2 multi-center OpACIN-neo trial, 86 stage III melanoma pts with resectable and RECIST 1.1 measurable lymph node metastasis were randomized between 3 different dosing schedules of neoadjuvant IPI + NIVO: arm A: 2x IPI3+NIVO1 Q3W (n = 30), arm B: 2x IPI1+NIVO3 Q3W (n = 30), and arm C: 2x IPI3 Q3W followed by 2x NIVO3 Q2W (n = 26). Lymph node dissection was scheduled at week 6. Primary endpoints were toxicity, radiologic RR and pRR; RFS and EFS were secondary endpoints. **Results:** After a median FU of 24.6 months, the median RFS and EFS was not reached in any of the 3 arms. In total, 2 pts progressed before surgery, 12 pts relapsed (11 pts without path response and 1 pt with pCR) and 5 pts died (4 due to melanoma and one pt due to toxicity). Estimated 24-months RFS was 84% (95% CI 76-92%) for the total population, 97% (95% CI 93-100%) for pts with a path response and 36% (95% CI 17-74%) for pts without a path response. Estimated 24-months EFS for the total population was 82% (95% CI 74-91%). RFS and EFS did not differ between the arms. Of the 81 pts alive, 55 (68%) have ongoing irAEs; only 2 (3%) pts have $\geq$ grade 3 irAEs. Most frequent ongoing irAEs were vitiligo (35%), fatigue (14%), sicca syndrome (11%), rash (10%), arthralgia (7%) and endocrine toxicities (20%). 17 pts need hormone replacement therapy: 11 (14%) thyroid hormone and 7 (9%) hydrocortisone. No difference between treatment arms was observed. Ongoing surgery-related AEs were observed in 31 (38%) pts of which lymphedema was seen most frequently (17 pts; 21%). **Conclusions:** Extended follow-up data shows that 2 cycles of neoadjuvant IPI + NIVO without adjuvant therapy induces durable RFS. While almost no ongoing high-grade irAEs were observed, the majority of pts have low-grade ongoing toxicities. These outcomes strongly support the need to test 2 cycles of neoadjuvant IPI1+NIVO3 versus adjuvant anti-PD-1 in a randomized phase 3 trial. Clinical trial information: NCT02977052. Research Sponsor: BMS.

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## 10016 Poster Discussion Session; Displayed in Poster Session (Board #365), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# Melanoma recurrence after adjuvant targeted therapy: A multicenter analysis.

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**Background:** Adjuvant targeted therapy (TT) improves relapse free survival (RFS) in patients (pts) with BRAF mutant stage 3 melanoma. The outcomes and optimal management of pts who relapse after adjuvant TT is unknown. **Methods:** Pts from 21 centres with recurrent melanoma after adjuvant TT were included. Disease characteristics, adjuvant therapy, recurrence, treatment at relapse and outcomes were examined. **Results:** 87 pts developed recurrent melanoma; 21 (24%) during and 66 (76%) after cessation of adjuvant TT. Median time to 1st recurrence was 16.3 months with median follow up after 1st recurrence of 31 months. 30 (34%) pts recurred locoregionally, 51 (59%) pts developed distant recurrence and 6 (7%) pts had both. Of those who recurred locoregionally, 23/30 (77%) pts underwent surgery to no evidence of disease, only 3 (13%) of which received adjuvant anti-PD1 therapy, and 15/30 (50%) subsequently developed distant disease. 29 (33.3%) pts have died. 75 (86%) pts received systemic therapy at either 1st or subsequent recurrence. 40 (46%) pts received 1st line anti-PD1 based therapy (single agent anti-PD1, anti-PD1 with ipilimumab or anti-PD1 with investigational agent), 12 (14%) pts received ipilimumab monotherapy, 18 (21%) pts received retreatment with combination BRAF/MEK inhibitors and 5 (6%) pts received other agents (chemotherapy, TVEC). 57 (66%) pts had disease that was assessable for response rate (RR). RR after relapse was 69.7% (23/33) to 1st line anti-PD-1 based therapy, 46% (6/13) to TT and 9% (1/11) to ipilimumab monotherapy (Table). Median overall survival (OS) from date of 1st recurrence for all pts was not reached. OS varied by drug class received as 1st line systemic therapy after relapse. 3 year OS was 79% for anti-PD-1 based therapy, 55% for TT and 25% for ipilimumab. **Conclusions:** This study demonstrates that pts who relapse after adjuvant TT may respond to subsequent immunotherapy at similar rates to the treatment naïve setting.
Research Sponsor: None.

**Response rate to first-line systemic therapy after recurrence.**

| | Anti-PD-1 +/- trial drug (N=19) | Ipilimumab + Nivolumab (N=14) | Targeted therapy (N=13) | Ipilimumab alone (N=11) |
|---|---|---|---|---|
| Complete Response | 4 | 5 | 2 | 1 |
| Partial Response | 9 | 5 | 4 | 0 |
| Stable Disease | 0 | 0 | 2 | 1 |
| Progressive Disease | 6 | 4 | 5 | 9 |
| Response Rate | **68%** | **71%** | **46%** | **9%** |

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## 10017 Poster Discussion Session; Displayed in Poster Session (Board #366), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# Final analysis of relapse-free survival in a multicenter, double-blind, placebo-controlled trial of seviprotimut-L polyvalent melanoma vaccine after resection of high-risk melanoma.

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**Background:** Seviprotimut-L is a vaccine prepared from antigens of 3 human melanoma cell lines, administered with alum. Prior formulations induced T cell and antibody responses and improved survival in a small phase II clinical trial. Part B1 of MAVIS (Melanoma Antigen Vaccine Immunotherapy Study, a three part, Phase III clinical program), was a multicenter, double-blind, placebo-controlled trial to assess efficacy of seviprotimut-L, with the primary endpoint of relapse-free survival (RFS). The goal of Part B1 was to guide design of the pivotal Part B2. **Methods:** Patients with AJCC v7 stage IIB-III cutaneous melanoma, after surgical resection, age 18-75, ECOG PS 0-1, were randomized 2:1 to seviprotimut-L 40 mcg or placebo, injected subcutaneously every 2 weeks x 5, then monthly x 4, then every 3 months x 9. Patients were stratified by stage (IIB/C, IIIA, IIIB/C). Target enrollment was 325. The study was powered for assessment of RFS, with target hazard ratio (HR) of 0.625, one-sided alpha of 0.10, and power 80%. Final data are presented. **Results:** 347 patients were randomized. Arms were well-balanced. Treatment-related adverse events (AEs) led to discontinuation in 0.4% and 0%, respectively, for vaccine and placebo arms. There were no treatment-related SAEs. By intent-to-treat (ITT) analysis, RFS was not significantly longer for seviprotimut-L in the full study population but trended toward benefit (HR 0.88). Subgroup analysis based on planned stratification revealed the hazard ratio (HR) for the Stage IIB/IIC subset (randomization stratum, n=111) to be 0.65 (95% CI [0.37, 1.17]), favoring seviprotimut-L. Age can decrease immune competence: RFS was longer with vaccine for patients age $<60$ overall (N = 191, HR = 0.64 [0.38, 1.08]) and among Stage IIB/C patients (N = 52, HR = 0.32 [0.12, 0.86]). The effect modification interaction p value for age for stage IIB/IIC patients was 0.056. In a multivariable RFS model, for IIB/IIC patients $<60$ with ulceration (n=38), HR = 0.209 [0.07,0.61]. For overall survival, for patients $< 60$, HR = 0.41 [0.33,1.14] (n=191, 19 deaths) and for those $\geq 60$, HR = 0.92 [0.39,2.12] (n = 156, 24 deaths). **Conclusions:** Seviprotimut-L is very well-tolerated. Subgroup efficacy analyses identified populations who may benefit from Seviprotimut-L: those with Stage IIB/IIC melanoma and those under age 60. These data support design of the definitive part B2 of the MAVIS phase III trial to test seviprotimut-L for stage IIB/C patients, with stratification by age and ulceration. Clinical trial information: NCT01546571. Research Sponsor: Polynoma.

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## 10018 Poster Discussion Session; Displayed in Poster Session (Board #367), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# Phase II study of cemiplimab in patients (pts) with advanced cutaneous squamous cell carcinoma (CSCC): Longer follow-up.

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**Background:** Cemiplimab monotherapy achieves clinically meaningful activity in pts with advanced CSCC (metastatic [mCSCC] or locally advanced [laCSCC] not amenable to curative surgery or curative radiation) and has a safety profile consistent with other anti–PD-1 agents. Based on initial data (median follow-up of 9.4 months in the pivotal study, NCT02760498), cemiplimab (cemiplimab-rwlc in the US) was approved for the treatment of pts with advanced CSCC. Historical data shows median overall survival (OS) of approximately 15 months with conventional chemotherapy or EGFR inhibitors (ASCO 2019, e21033). We present ~1-year additional follow-up from the largest prospective data set in advanced CSCC. **Methods:** Pts received cemiplimab 3 mg/kg Q2W (Group [Gp] 1; mCSCC; Gp 2, laCSCC) or cemiplimab 350 mg Q3W (Gp 3, mCSCC). The primary endpoint was objective response rate (ORR; complete response + partial response) per independent central review (ICR). Data presented here are per investigator review (INV); ICR data will be available at the meeting. **Results:** 193 pts were enrolled (Gp 1, n = 59; Gp 2, n = 78; Gp 3, n = 56). 128 pts had received no prior anti-cancer systemic therapy, 65 pts were previously treated. As of Oct 11, 2019 (data cut-off), median duration of follow-up was 15.7 months (range: 0.6–36.1) among all pts; 18.5 months (range: 1.1–36.1) for Gp 1, 15.5 months (range: 0.8–35.0) for Gp 2, and 17.3 months (range: 0.6–26.3) for Gp 3. ORR per INV was 54.4% (95% CI: 47.1–61.6) for all pts; 50.8% (95% CI: 37.5–64.1) for Gp 1, 56.4% (95% CI: 44.7–67.6) for Gp 2, and 55.4% (95% CI: 41.5–68.7) for Gp 3. ORR per INV was 57.8% (95% CI: 48.8–66.5) among treatment-naïve pts and 47.7% (95% CI: 35.1–60.5) among previously treated pts. Median duration of response (DOR) has not been reached (observed DOR range: 1.8–34.2 months). In responding pts, estimated proportion of pts with ongoing response at 24 months was 76.0% (95% CI: 64.1–84.4). Median OS has not been reached. Estimated OS at 24 months was 73.3% (95% CI: 66.1–79.2). The most common treatment-emergent adverse events (TEAEs) by any grade were fatigue (34.7%), diarrhea (27.5%), and nausea (23.8%). The most common grade ≥3 TEAEs were hypertension (4.7%) and anemia and cellulitis (each 4.1%). **Conclusions:** For pts with advanced CSCC, cemiplimab achieves ORRs, DOR and survival superior to what has been reported with other agents. Clinical trial information: NCT02760498. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

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## 10019 Poster Discussion Session; Displayed in Poster Session (Board #368), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# CheckMate 067: Long-term outcomes in patients with mucosal melanoma.

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**Background:** Mucosal melanoma is a rare but aggressive malignancy with a poor prognosis. Here we report 5-y outcomes in a subgroup of patients with mucosal melanoma treated in CheckMate 067 with nivolumab plus ipilimumab (NIVO+IPI), NIVO alone, or IPI alone. **Methods:** Patients with previously untreated stage III or IV melanoma were randomized 1:1:1 to receive NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W followed by NIVO 3 mg/kg Q2W, NIVO 3 mg/kg Q2W + placebo, or IPI 3 mg/kg Q3W for 4 doses + placebo until progression or unacceptable toxicity. Mucosal histology was not a stratification factor, and patients with mucosal melanoma were identified by local investigators in the study. Descriptive subgroup analyses were performed to evaluate efficacy (objective response rate [ORR], progression-free survival [PFS], overall survival [OS]), and safety. **Results:** A total of 79 patients with mucosal melanoma were treated. With a minimum follow-up of 60 mo, NIVO+IPI treatment was associated with the highest 5-y ORR (43% [vs 30% with NIVO and 7% with IPI]), PFS (29% [vs 14% and 0%, respectively]), and OS (36% [vs 17% and 7%, respectively]; Table), consistent with trends in the intent-to-treat (ITT) population; however, efficacy outcomes were generally less favorable overall relative to the ITT population. Complete response rates were higher with NIVO+IPI (14%) relative to monotherapy (NIVO, 4%; IPI, 0%) in patients with mucosal melanoma. Safety outcomes, including the grade 3/4 treatment-related adverse event rates of 54%, 26%, and 25%, respectively, were similar to the ITT population. **Conclusions:** This 5-y analysis showed that patients with mucosal melanoma in CheckMate 067 had similar safety outcomes but poorer long-term efficacy vs the ITT population. Patients with mucosal melanoma treated with NIVO+IPI appeared to have more favorable survival outcomes than those treated with NIVO or IPI alone. Novel therapies are needed to further improve long-term benefit in patients with mucosal melanoma. Clinical trial information: NCT01844505. Research Sponsor: Bristol-Myers Squibb, Grant (P30CA008748, to Dr. Wolchok) from the National Cancer Institute, and a grant (to Dr. Larkin) from the National Institute for Health Research Royal Marsden–Institute of Cancer Research Biomedical Research Centre.

| | Mucosal | | | ITT[a] | | |
|---|---|---|---|---|---|---|
| **NIVO+IPI (n = 28)** | NIVO (n = 23) | IPI (n = 28) | NIVO+IPI (n = 314) | NIVO (n = 316) | IPI (n = 315) | |
| **ORR, %** | 43 | 30 | 7 | 58 | 45 | 19 |
| **(95% CI)** | (24–63) | (13–53) | (1–24) | (53–64) | (39–50) | (15–24) |
| **PFS** | | | | | | |
| **Median, mo** | 5.8 | 3.0 | 2.6 | 11.5 | 6.9 | 2.9 |
| **(95% CI)** | (2.7–19.3) | (2.5–13.9) | (2.6–2.8) | (8.7–19.3) | (5.1–10.2) | (2.8–3.2) |
| **5-y rate, %** | 29 | 14 | 0 | 36 | 29 | 8 |
| **(95% CI)** | (13–48) | (4–32) | | (31–42) | (24–35) | (5–12) |
| **OS** | | | | | | |
| **Median, mo** | 22.7 | 20.2 | 12.1 | NR | 36.9 | 19.9 |
| **(95% CI)** | (5.6–NR) | (5.6–33.6) | (6.4–20.2) | (38.2–NR) | (28.2–58.7) | (16.8–24.6) |
| **5-y rate, %** | 36 | 17 | 7 | 52 | 44 | 26 |
| **(95% CI)** | (19–53) | (5–35) | (1–20) | (46–57) | (39–50) | (22–31) |

NR, not yet reached. [a]Larkin J, et al. *N Engl J Med* 2019:381:1535–1546.

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## 10020 Poster Discussion Session; Displayed in Poster Session (Board #369), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# Heterogeneous response and irAE patterns in advanced melanoma patients treated with anti-PD-1 monotherapy from different ethnic groups: Subtype distribution discrepancy and beyond.

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**Background:** Programmed cell death receptor-1 (PD-1) monotherapy is the standard first line therapy for advanced cutaneous melanoma, with efficacy, toxicity, and their correlations well established. Yet these remain poorly characterized for non-Caucasians and for certain rarer melanoma subtypes. **Methods:** Clinical data from melanoma patients treated with anti-PD-1 monotherapy between 2009 and 2018 was collected retrospectively from three independent institutions from the US and China. Tumor response, survival outcome, and organ/system-specific immune-related adverse effects (irAEs) were directly compared between different subgroups. **Results:** Among 626 patients, 411 were Caucasian, 214 non-Caucasian; 369 had cutaneous melanoma, and 257 other subtypes. Both ethnicity and melanoma subtype were independently associated with benefit and irAEs. In multivariate analyses, Caucasians had significantly higher objective response rate (ORR) (OR 2.0, 95% CI 1.1-3.5), but this did not translate into a survival advantage (PFS, HR 0.8, 95% CI 0.6-1.1; OS, HR 1.0, 95% CI 0.7-1.4); melanoma of unknown primary shared similar response and survival profile with cutaneous, while acral (ORR, OR 0.4, 95% CI 0.2-0.9; PFS, HR 1.6, 95% CI 1.1-2.2; OS, HR 1.3, 95% CI 0.8-1.9), mucosal (ORR, OR 0.4, 95% CI 0.2-0.9; PFS, HR 1.4, 95% CI 1.0-2.0; OS, HR 1.7, 95% CI 1.1-2.6) and ocular (ORR, OR 0.1, 95% CI 0-0.6; PFS, HR 2.3, 95% CI 1.4-3.6; OS, HR 2.2, 95% CI 1.3-3.6) melanomas had inferior outcomes. Non-Caucasian cutaneous patients had a significantly worse ORR than Caucasians with cutaneous melanoma ($P < .01$). Distinct irAE patterns were observed, exemplified by lower incidence of most irAEs (although more frequent pneumonitis) in Caucasians, and higher and lower liver irAE incidence in ocular and mucosal melanomas, respectively. Endocrine, musculoskeletal and skin irAEs were associated with improved PFS and OS across ethnicities and nearly all melanoma subtypes, whereas heterogeneity existed for other irAE types. **Conclusions:** Ethnicity and melanoma subtype are associated with distinct response patterns, survival outcomes, and irAE profiles in the setting of anti-PD-1 monotherapy. More research is needed to elucidate the molecular and immunologic determinants of these variable outcomes. Research Sponsor: None.

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## 10021 Poster Discussion Session; Displayed in Poster Session (Board #370), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# The IMPemBra trial, a phase II study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in melanoma patients harboring the BRAFV600 mutation.

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**Background:** Continuous combination of MAPK inhibition (MAPKi) and anti-PD-(L)1 has been investigated by several trials to improve outcome of BRAFV600 mutated melanoma patients. A major obstacle for continuous combination is the high frequency (~60%) of grade 3-4 treatment-related adverse events (TRAE) for which many patients need to discontinue (~40%). In a preclinical model we showed that short-time MAPKi induces T cell infiltration and is synergistic with anti-PD-1. In patients T cell infiltration increased after short-term MAPKi, while after $>$ 2 weeks this was often diminished. The aim of this phase 2b study was to identify the optimal duration of MAPKi with dabrafenib (BRAFi) + trametinib (MEKi) in combination with pembrolizumab (anti-PD-1) in terms of safety, feasibility and immune-activating capacity. **Methods:** Treatment-naïve BRAFV600E/K mutant advanced melanoma patients started pembrolizumab (PEM) 200mg Q3W and were randomized in week 6 to continue PEM only (cohort 1) or to receive in addition intermittent dabrafenib (D) 150 mg BID + trametinib (T) 2mg QD for 2 x 1 week (cohort 2), 2 x 2 weeks (cohort 3), or continuous for 6 weeks (cohort 4). All cohorts continued PEM for up to 2 years. Primary endpoints were safety and treatment-adherence. Secondary endpoints were objective response rate (ORR, RECIST 1.1) at week 6, 12, 18 compared to baseline and PFS. **Results:** Between June 2016 and August 2018, 32 patients have been included; 56% were male, 50% had M1c disease and the majority had a BRAFV600E mutation (81%) and a baseline LDH level $>$ ULN (87%). Grade 3-4 TRAE were observed in 12%, 12%, 50%, and 62% of patients in cohort 1, 2, 3, and 4, respectively. All planned D+T was given in 88%, 63%, and 38% of patients in cohort 2, 3, and 4. Most patients needed to interrupt or discontinue D+T due to fever or elevated liver enzymes. ORR at week 6, week 12, and week 18 were 38%, 62%, and 62% in cohort 1, 25%, 62%, and 75% in cohort 2, 25%, 50%, and 75% in cohort 3 and 0%, 62%, and 50% in cohort 4. After a median follow-up of 17.4 months, the median PFS of patients treated with PEM monotherapy was 10.6 months compared to 27.0 months for patients treated with PEM and short-term/intermittent D+T ($p = 0.13$). **Conclusions:** Combination of PEM plus intermittent D+T seems more feasible and tolerable than continuous triple therapy. Intermittent short-time combination therapy might be equally effective, enables therapy with MAPKi as a second line, and therefore warrants further investigation in a larger patient cohort. Clinical trial information: NCT02625337. Research Sponsor: MSD.

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## 10022 Poster Discussion Session; Displayed in Poster Session (Board #371), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# A phase II, multicenter study of encorafenib/binimetinib followed by a rational triple-combination after progression in patients with advanced BRAF V600-mutated melanoma (LOGIC2).

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**Background:** LOGIC2 evaluates the benefit of a 3rd agent added to encorafenib (enco)/binimetinib (bini), selected at progression based on the genetic tumor evolution. **Methods:** In part I/run-In, pts were treated with enco/bini until disease progression (as defined per RECIST v1.1). Foundation One NGS was applied on a baseline sample and on a PD sample. Based on the genetic evolution between the biopsy at inclusion (bxI) and at progression (bxPD) and clinical considerations, pts entered part II and received one of four 3rd agent additions to enco/bini combinations: A. LEE011 (CDK4/6 inhibitor), B. BKM120 (PI3K inhibitor), C. INC280 (c-Met inhibitor), or D. BGJ398 (FGFR inhibitor). An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle was used to make dose escalation decisions. Assessments include objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and safety. Data cutoff for this analysis was May 12, 2019. Data is as is. Part 1 of study is ongoing. Part 2 of study is closed to enrollment. **Results:** 58 pts enrolled into part II (group A=38; B=6; C=13; D=1). 29 pts were assigned to treatment based on bxPD results (Table). In groups A, B, and C, the confirmed ORR was 5.3%, 0%, and 0%, and the DCR was 26.3%, 16.7%, and 15.4%, with median PFS of 2.1, 1.6, and 2.2 months, respectively. Safety was consistent with known profiles of the individual agents. **Conclusions:** Triple therapy is feasible when a 3rd agent is added to enco/bini at progression based on genetic alterations, although activity observed was low. Further exploration to identify patterns of resistance susceptible to the addition of a 3rd agent is needed. Gene alterations for enrollment into part 2. Clinical trial information: NCT02159066. Research Sponsor: Pfizer Inc.

| 3rd agent | Gene symbol | Mutations (amino acid change, (n)) | Amplification[§] n | Loss of copy[¥] n | Total Alterations (n=29) |
|---|---|---|---|---|---|
| **A. LEE011** | KRAS | A146V (n=1) | | | 1 |
| | NRAS | Q61R (n=2), Q61K (n=4)* | | | 6 |
| | HRAS | G13R (n=1) | | | 1 |
| | CDKN2A | splice site 151-1G>A (n=2), V126D (n=1), D146fs*12+ (n=1), E61* (n=1), Y44fs*1 (n=1) | 7 | | 13 |
| | BRAF | 2 | | | 2 |
| | CDK4 | R24H (n=1) | | | 1 |
| | MAP2K1 | F53I (n=1) | | | 1 |
| **B. BKM120** | | PTEN | 1 | | 1 |
| | PIK3CA | M1043V(n=1) | | 1 | |
| **C. INC280** | | MET | 2 | | 2 |

*1 patient has both Q61K and Q61R [§]Amplication = copy number ratio >1, [¥]Loss of copy= copy number ratio < 1.

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## 10023 Poster Discussion Session; Displayed in Poster Session (Board #372), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

# Time to central nervous system (CNS) metastases (mets) with atezolizumab (A) or placebo (P) combined with cobimetinib (C) + vemurafenib (V) in the phase III IMspire150 study.

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**Background:** The phase 3 IMspire150 study (NCT02908672) demonstrated improved progression-free survival with first-line combination treatment with A+C+V vs P+C+V in patients (pts) with previously untreated *BRAF*$^{V600}$ mutation–positive advanced melanoma. Here we report incidence and time to development of CNS mets with A+C+V vs P+C+V in the IMspire150 study. **Methods:** Eligible pts were randomized 1:1 to receive A+C+V or P+C+V. A or P were given on day 1 and 15 of each 28-day cycle after an initial cycle of C+V. Incidence and time to development of CNS mets were evaluated in pts with no history of CNS mets at baseline confirmed by magnetic resonance imaging/computed tomography (MRI/CT). On study MRI/CT assessments were performed as clinically indicated. Time-to-event outcomes were estimated using the Kaplan-Meier method and competing risks analysis. Sensitivity analyses were conducted using landmark analysis at time of initiation of A or P. **Results:** 514 pts were randomized to receive A+C+V (n = 256) or P+C+V (n = 258); 244 and 247 pts, respectively, had no history of CNS mets at baseline. After a median follow-up of 18.9 months, CNS mets had developed in 52/244 pts (21%) in the A+C+V arm and 62/247 pts (25%) in the P+C+V arm. In both arms, pts with CNS mets were more likely to have other known unfavorable prognostic factors: elevated LDH, presence of liver mets, and/or higher tumor burden. Cumulative incidence of CNS mets as first site of progressive disease with A+C+V vs P+C+V was 8% vs 9%, 16% vs 19%, 20% vs 24%, and 23% vs 26% at 6, 12, 18, and 24 months, respectively (hazard ratio [HR] 0.87; 95% CI 0.60-1.26). Estimated CNS mets-free survival rates for A+C+V vs P+C+V were 91% vs 90%, 81% vs 75%, 74% vs 66%, and 69% vs 62% at 6, 12, 18, and 24 months, respectively, with a trend for improved CNS mets-free survival with A+C+V (HR 0.79; 95% CI 0.55-1.14). Results of landmark analyses for CNS mets-free survival and cumulative incidence of CNS mets were similar to those in the overall analysis. **Conclusions:** The addition of anti–programmed death-ligand 1 to C+V is associated with numerically lower rates of interval development of CNS mets, consistent with the overall benefit observed for A+C+V in the study. This finding requires further follow-up to fully assess the magnitude of benefit of A+C+V on CNS mets-free survival. Clinical trial information: NCT02908672. Research Sponsor: F. Hoffmann-La Roche Ltd.

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**10024** **Poster Session (Board #373), Fri, 8:00 AM-11:00 AM**

## The impact of BRAF mutation status on clinical outcomes with single-agent PD-1 inhibitor versus combination ipilimumab/nivolumab.

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**Background:** Nearly half of all metastatic melanoma patients possess the BRAF V600 mutation. Several therapies are approved for BRAF mutant metastatic melanoma, but it is unclear if there is a differential outcome to various immunotherapy regimens. Our aim was to better assess if BRAF mutation status has any impact on survival to combination ipilimumab/nivolumab (I/N) versus single-agent PD-1 inhibitor (PD-1i). **Methods:** We performed a single center, retrospective analysis on a cohort of patients diagnosed with metastatic or unresectable melanoma from 2012 to 2019 at the University of Michigan who were treated with standard I/N or PD-1i (nivolumab or pembrolizumab). A univariate analysis of progression free survival (PFS) and overall survival (OS) was stratified by treatment type and BRAF mutation status. A multivariate Cox regression of survival was used to compare the effects of the treatment groups adjusted by BRAF status, age, gender, pre-treatment LDH level, prior treatment status, and brain metastases status. **Results:** 323 patients were identified. 132 had BRAF V600 mutation and 191 had BRAF wildtype (WT) status. 138 patients received I/N and 185 patients received PD-1i. In our univariate analysis, there was no difference in PFS [HR: 0.72, 95% CI, 0.46 – 1.13] or OS [HR: 0.78, 0.44 – 1.38] with I/N versus PD-1i in the BRAF mutant cohort, but there was improved PFS [HR: 0.55, 0.35 – 0.88) and OS [HR: 0.52, 0.28 – 0.95] with I/N compared to PD-1i in the BRAF WT group. In the multivariate analysis, the BRAF WT group continued to show PFS benefit with I/N compared to PD-1i [HR: 0.57, 95% CI, 0.35 – 0.95], but the OS benefit no longer achieved statistical significance [HR: 0.54, 0.28 – 1.03]. **Conclusions:** Our study results were discordant with the observation in the landmark CheckMate 067 trial, which noted improved PFS and OS with I/N compared to nivolumab alone in the BRAF mutant group and no difference in the BRAF WT group. In our real-world retrospective analysis, I/N over PD-1i should be considered as initial immunotherapy for metastatic melanoma patients regardless of BRAF mutation status, but even more favorably in BRAF WT. Research Sponsor: None.

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**10025** **Poster Session (Board #374), Fri, 8:00 AM-11:00 AM**

## Initial report of treatment of uveal melanoma with hepatic metastases with yttrium90 internal radiation followed by ipilimumab and nivolumab.

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**Background:** Hepatic metastases from uveal melanoma have no established therapy, with a median survival of only 6-12 months. To date therapy with checkpoint inhibitors has yielded minimal results. To take advantage of possible synergy between radiation and immunotherapy we treated patients with yttrium90 internal radiation followed by immunotherapy. **Methods:** Patients received yttrium90 (SirSpheres) via hepatic artery infusion in two treatments, one to each lobe 3-4 weeks apart, followed in 3-6 weeks by ipilimumab and nivolumab for 4 doses, then nivolumab maintenance. **Results:** We are presenting interim results because of the excessive toxicity seen when these FDA-approved modalities were used in sequence with the FDA-approved dosages. Initially dosing of yttrium90 (Y90) followed the package insert "BSA method" but after 8 patients we had 5 cases of grade 3-4 hepatic toxicity; in 4 cases the toxicity was observed after just the Y90. One case of cirrhosis occurred in a patient whose liver received 40-45Gy; her cirrhosis was felt most likely due to the Y90. Y90 dosing was then reduced to limit dosage to normal liver to 35Gy, and none of the next 5 patients have had more than grade 2 hepatic toxicity. Dosage to the normal liver is approximated by the MIRD formula: Actual delivered liver dose [Gy] = 50 * Administered activity [GBq] * (1 – Lung shunt fraction) / kg of treated liver. If calculated dose was $>$ 35GY, dosage in GBq is reduced proportionally. Toxicity in the first 5 patients to receive immunotherapy included one grade 4, two grade 3 and two grade 2 hepatic toxicities, and only 3 of the 5 patients received more than one dose of ipilimumab. We then reduced dosing of ipilimumab from 3mg/kg x 4 to 1mg/kg x 4 because of this excessive autoimmune toxicity. Of 13 patients, 10 received both Y90 and immunotherapy, and 3 had responses (1 CR, 2 PR) with 3 patients stable $>$ 5months. Median progression-free survival for all patients is 27 weeks and median overall survival is greater than 48 weeks. Treatment with Y90 produced an over 50% fall in peripheral blood lymphocytes which was reversed in most patients by the immunotherapy. **Conclusions:** With dose modifications this therapy appears feasible and objective tumor responses were seen. Sequential therapy with Y90 and immunotherapy appears tolerable if radiation to normal liver is limited to 35Gy and ipilimumab dose is 1mg/kg. Clinical trial information: NCT02913417. Research Sponsor: California Pacific Medical Foundation.

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**10026** **Poster Session (Board #375), Fri, 8:00 AM-11:00 AM**

## Combination anti-PD-1 and ipilimumab (ipi) therapy in patients with advanced melanoma and pre-existing autoimmune disorders (AD).

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**Background:** Clinical trials of immunotherapy exclude patients (pts) with pre-existing AD. While retrospective data exist regarding the efficacy and safety of single agent ipi and anti-PD1 antibodies (PD1) in pts with AD, no data are available regarding the safety and efficacy of combination therapy in pts with AD, which has a higher toxicity risk. **Methods:** Pts with melanoma and pre-existing AD treated with combination ipi/PD1 were retrospectively identified from 10 international centres. Data regarding AD, treatment, toxicity and outcomes were examined. **Results:** Fifty-five pts were included, 46 were treated with ipi/nivolumab and 9 with ipi/pembrolizumab. 40 had an ipi dose of 3mg/kg while 15 had a lower dose regimen. 9 pts received prior PD1 therapy; 3 suffered moderate immune-related adverse events (irAE) with no flares of AD on single agent PD1. Pre-existing AD included inflammatory bowel disease (IBD), thyroiditis, rheumatoid arthritis (RA), multiple sclerosis and psoriasis. 10 pts had active symptoms of AD and 13 were immunosuppressed at commencement of ipi/PD1. Eighteen pts (33%) experienced a flare of their AD including 4/7 with RA, 3/6 with psoriasis, 5/9 with IBD, 3/18 with thyroiditis, 1/1 with Sjogren's syndrome, 1/1 with polymyalgia, 1/1 with Behcet's syndrome. Median time to flare was 19 days (range 4 – 167). 13 pts were managed with steroids, 5 required additional immunosuppressants. 7 pts were hospitalised for management of flare (5 with IBD, 2 with RA). 2 pts required intensive care and vasopressors for severe IBD flare, quiescent prior to ipi/PD1. One for diarrhoea and shock and one for duodenal perforation. 8 pts ceased treatment due to flare (3 with IBD, 2 with RA, 1 with Behcet's, 1 with Sjogren's). Thirty-seven pts (67%), experienced an irAE unrelated to their AD, 38% G3 or G4. The most frequent irAEs were colitis (n = 16), hepatitis (n = 12), endocrinopathies (n = 12), with 13 pts experiencing an irAE in $\geq$ 2 organs. 9 pts experienced both AD flare and an irAE. 20 pts (36%) ceased immunotherapy due to irAEs. ORR was 55% (54% in PD1 naive pts), at a median follow up of 14 months, 77% of responses ongoing. ORR in pts who had a flare of their AD was 44% and in pts on immunosuppression was 46%. Median PFS was shorter in pts who had a flare of AD compared with those who did not (2.6 vs 9 months; P-value 0.047). **Conclusions:** Combination ipi/PD1 shows efficacy comparable to clinical trial populations in pts with pre-existing AD and advanced melanoma. Whilst there was a substantial risk of flare of AD, no increased frequency of irAE's was observed. Research Sponsor: None.

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**10028** **Poster Session (Board #377), Fri, 8:00 AM-11:00 AM**

## The anti–PD-1 antibody spartalizumab in combination with dabrafenib and trametinib in advanced *BRAF* V600–mutant melanoma: Efficacy and safety findings from parts 1 and 2 of the Phase III COMBI-i trial.

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**Background:** Treatment (tx) with checkpoint inhibitors or targeted therapy improves outcomes in patients (pts) with *BRAF* V600–mutant advanced melanoma; however, many pts subsequently progress and die. Preliminary evidence suggests that targeted therapy may enhance the impact of checkpoint inhibitors and improve efficacy compared with either treatment alone. **Methods:** COMBI-i is investigating first-line spartalizumab 400 mg every 4 wk + dabrafenib 150 mg twice daily + trametinib 2 mg once daily in pts with unresectable or metastatic *BRAF* V600–mutant melanoma (NCT02967692). We report efficacy and safety data from parts 1 (run-in cohort) and 2 (biomarker cohort), with a median follow-up of 24.3 mo. Response was assessed per RECIST v1.1. The randomized part 3 is ongoing. **Results:** 36 pts were enrolled (part 1: n = 9; part 2: n = 27); 20 (56%) had stage IV M1c disease and 15 (42%) had elevated lactate dehydrogenase (LDH) levels (≥ upper limit of normal). At the data cutoff (August 19, 2019), tx was ongoing in 10 pts (28%). The confirmed investigator-assessed objective response rate (ORR) was 78% (n = 28), with 16 complete responses (CRs; 44%) and 12 partial responses (33%). Median duration of response (DOR; 10/28 responders with events) was not reached (NR); 24-mo DOR rate was 53.4% (95% CI, 29%-73%). Median progression-free survival (PFS) was 22.7 mo; 24-mo PFS rate was 41.4% (95% CI, 23%-59%). At the cutoff, median overall survival (OS) was NR, with a 24-mo OS rate of 74.1% (95% CI, 56%-86%). In pts with elevated LDH, ORR was 67%, with 4 CRs (27%); median PFS was 10.7 mo (95% CI, 4.6-19.1 mo), and median OS was NR. The estimated 24-mo PFS and OS rates in these pts were 26.7% and 52.5%, respectively. All pts had ≥ 1 tx-related adverse event (TRAEs); 26 (72%) had grade ≥ 3 TRAEs. The most common grade ≥ 3 TRAEs were pyrexia (17%), increased lipase (11%), neutropenia (11%), increased blood creatine phosphokinase (8%), and increased γ-glutamyltransferase (8%). AEs leading to discontinuation of all 3 study drugs occurred in 6 pts (17%). All-causality grade ≥ 3 AEs requiring immunosuppressive medication occurred in 19 pts (53%). One pt died of cardiac arrest that was not considered tx related. **Conclusions:** The combination of spartalizumab + dabrafenib + trametinib resulted in high ORR and CR rates, with a high frequency of durable responses, including in patients with poor prognostic factors. Clinical trial information: NCT02967692. Research Sponsor: Novartis Pharmaceuticals Corporation.

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**10029** **Poster Session (Board #378), Fri, 8:00 AM-11:00 AM**

## Association between complete response and survival in advanced melanoma treated with talimogene laherparepvec (T-VEC) plus ipilimumab (ipi).

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**Background:** This is the first randomized trial testing the addition of an oncolytic virus to an immune checkpoint inhibitor for advanced melanoma. At the 3-year (yr) follow-up, the combination (combo) of T-VEC and ipi demonstrated durable and statistically superior objective response rate (ORR) over ipi alone (36.7% vs. 16.0%; odds ratio, 3.0; 95% CI, 1.6–6.0; $P = 0.002$). Complete response (CR) rate was 21.4% with the combo and 6.0% with ipi. Median overall survival (OS) was not reached in either arm. In this post hoc analysis, we utilized the 3-yr landmark data to explore the relationship between CR and OS in the combo arm. **Methods:** Pts with unresectable, stage IIIB-IV melanoma were randomized 1:1 to receive combo or ipi alone. T-VEC was administered intratumorally on day 1 of week (wk) 1 at $10^6$ plaque-forming units (PFU)/mL followed by subsequent doses at $10^8$ PFU/mL on day 1 of wk 4, and every 2 wks thereafter. Ipi (3 mg/kg) was given every 3 wks starting on day 1 of wk 6 for up to 4 doses. Response was assessed by investigators per immune-related response criteria every 12 wks until disease progression. The primary endpoint was ORR; key secondary endpoints were OS, progression-free survival, and safety. **Results:** 198 pts were randomized (98 to combo; 100 to ipi). As of February 25, 2019, the median follow-up time was 40.0 mos (range: 0.2–63.7) for the combo arm. Among 98 pts who received combo, 21 (21.4%) had a best overall response of CR including 8 who converted from an initial partial response (PR), 15 (15.3%) had PR, 19 (19.4%) had stable disease, 30 (30.6%) had progressive disease, and 13 (13.2%) were unevaluable. Of 21 pts achieving CR, 17 (81%) had ECOG status of 0, 16 (76.2%) had stage IIIB-IVM1a disease, and 16 (76.2%) had no visceral metastases. Median duration of CR was not reached (range: 5.4[+]–58.2[+] mos); 19 of 21 CRs lasted more than 6 months. The baseline tumor burden was lower in pts with CR than in those with non-CR. Median OS was not reached in pts with CR (range: 25.1[+]–63.7[+] mos) and was 47.6 mos (range: 0.2[+]– 63.7 [+] mos) in pts with non-CR (Log-rank $P = 0.0005$). The Kaplan–Meier estimated 3-year OS rate was 100.0% for patients with CR and 52.3% for those with non-CR. **Conclusions:** CR rate was higher with T-VEC plus ipi than with ipi alone in pts with advanced melanoma (21.4% vs. 6.0%). In the combo arm, CR was associated with prolonged OS, and pts with CR tended to have better ECOG performance status, earlier-stage disease, and lower baseline tumor burden, as compared with those with non-CR. Clinical trial information: NCT01740297. Research Sponsor: Amgen Inc.

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**10030** **Poster Session (Board #379), Fri, 8:00 AM-11:00 AM**

## Surrogate endpoints for overall survival in anti-programmed death-1 and anti-programmed death ligand 1 trials of advanced melanoma.

*Run-Cong Nie, Shu-Qiang Yuan, Yuanfang Li, Yingbo Chen, Zhiwei Zhou; Sun Yat-Sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China*

**Background:** The mechanisms of action of anti-PD-1/PD-L1 agents are markedly distinct from those of cytotoxic agents, thus a critical issue that is under investigation is what is the optimal endpoint and how should tumor response be evaluated in anti-PD-1/PD-L1 trials for metastatic melanoma. Here, we assessed surrogacy of objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS) for overall survival (OS) in anti-PD-1/PD-L1 trials of metastatic melanoma through a meta-analysis of randomized controlled trials (RCTs). **Methods:** PubMed and EMBASE were searched for phase 2/3 RCTs till June 2019 investigating anti-PD-1/PD-L1 agents. Treatment effect (hazard ratio or odds ratio) on potential surrogates (ORR/DCR/PFS) and OS were collected. At trial level, we assessed the correlation between treatment effect on potential surrogates and OS, weighted by sample size, fixed and random effect models, and calculated the surrogate threshold effect (STE). Sensitivity analyses and leave-one-out cross-validation approach were performed to evaluate the robustness of our findings. **Results:** We included 8 RCTs (4,110 patients; 11 comparisons). We did not identify strong correlations between ORR (coefficient of determination [$R^2$]: 0.09 to 0.25), DCR (0.41 to 0.57) and OS. However, we noted a strong correlation between PFS and OS, with $R^2$ of 0.82 in sample size, 0.75 in fixed effect, and 0.72 in random effect model weighting, the robustness of which was further verified by leave-one-out cross-validation approach. Sensitivity analyses with restriction to trials with less than 50% crossover ($R^2$: 0.94-0.94), phase 3 trials ($R^2$: 0.94-0.95), large trials ($R^2$: 0.78-0.86) and first-line trials ($R^2$: 0.83-0.91) strengthened the correlation. The STE for PFS was 0.78. **Conclusions:** PFS may be the appropriate surrogate for OS in anti-PD-1/PD-L1 trials of metastatic melanoma. A future anti-PD-1/PD-L1 trial would need less than 0.78 for PFS of the upper limit of confidence interval to predict an OS benefit. Research Sponsor: None.

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**10031** **Poster Session (Board #380), Fri, 8:00 AM-11:00 AM**

## Does body mass index really predict the response to systemic therapies in metastatic melanoma: A multicenter study from the MelBase French National Cohort?

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**Background:** Obesity is an established risk factor for several cancers and higher body mass index (BMI) is associated with poor prognosis. These data are still debated in melanoma. Furthermore, recently the concept of "obesity paradox" has emerged. In a large cohort published by *McQuade JL et al*, higher BMI was associated with better survival in patients with metastatic melanoma (MM) especially for those treated with targeted therapy (TT) and immune checkpoint inhibitors (ICI). We studied the association between BMI and progression-free survival (PFS) and overall survival (OS) in patients with MM treated with systemic therapies. **Methods:** This study was conducted from the prospective MelBase cohort (NCT02828202). Patients with MM treated with first-line ICI, TT, or CT were included. BMI was categorized by WHO criteria. Underweight patients were excluded. The co-primary outcomes were the associations between BMI and PFS or OS, stratified by treatment, sex and age. Multivariate analyses were performed. **Results:** A total of 1214 patients were analyzed. The majority of them were treated with ICI, followed by TT. Obese patients represented 22% of cohort (Table). Median follow-up was 13.5 months. The patients who were overweight or obese did not have different PFS ($p = 0.88$) or OS ($p = 0.25$) than patients with normal BMI. Stratifying this cohort by treatment received, age, sex and others parameters (such as LDH, number of metastatic site) did not revealed any difference. Multivariate analysis did not change the results. **Conclusions:** BMI was not associated with clinical outcomes in our cohort, especially in ICI and TT groups. Thus, we did not confirm the results presented by *McQuade JI et al.* with a cohort quite similar in term of size. Because BMI is too simplistic and then an imperfect measure of body composition, the published data are not reproducible. We caution the oncologists, about BMI as valuable predictive marker of survival for melanoma patients.
Research Sponsor: None.

| Characteristics at baseline | Whole population | 18.5 < BMI < 24.9 Normal | 25 < BMI < 29.9 Overweight | 30 < BMI Obese |
|---|---|---|---|---|
| Number of patients | 1214 | 516 | 429 | 269 |
| Age, years (mean) | 63.8 | 62.4 | 65.4 | 63.8 |
| Sex | 738 | 281 | 299 | 158 |
| Men | 476 | 235 | 130 | 111 |
| Women | | | | |
| AJCC 7th edition | 479 | 184 | 168 | 127 |
| III/M1a/M1b | 735 | 334 | 260 | 141 |
| M1c | | | | |
| Brain metastases | 228 | 112 | 75 | 41 |
| Yes | | | | |
| ECOG PS | 772 | 329 | 283 | 160 |
| 0 | 338 | 142 | 113 | 83 |
| ≥1 | | | | |
| Mutations Status | 469 | 211 | 156 | 102 |
| BRAFV600 | 219 | 86 | 86 | 47 |
| NRAS | | | | |
| LDH | 603 | 249 | 214 | 140 |
| Normal | 351 | 145 | 122 | 84 |
| High | | | | |
| First line treatment | 761 | 308 | 278 | 175 |
| Immune checkpoint inhibitors | 389 | 173 | 135 | 81 |
| Target therapy | 64 | 35 | 13 | 16 |
| Chemotherapy | | | | |

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**10032** **Poster Session (Board #381), Fri, 8:00 AM-11:00 AM**

## Surgery for unresectable stage IIIC and IV melanoma in the era of new systemic therapy.

*Stephanie Blankenstein, Maureen J.B. Aarts, Franchette van den Berkmortel, Marye Boers-Sonderen, Alfonsus Johannes Maria van den Eertwegh, Margreet G. Franken, Jan Willem de Groot, John B. A. G. Haanen, Geke Hospers, Ellen Kapiteijn, Djura Piersma, Rozemarijn Van Rijn, Karijn Suijkerbuijk, Albert J. ten Tije, Astrid Aplonia Maria Van Der Veldt, Gerard Vreugdenhil, Michel W.J.M. Wouters, Alexander Christopher Jonathan Van Akkooi; Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Maastricht University Medical Center, Maastricht, Netherlands; Zuyderland Hospital, Heerlen, Netherlands; Radboudumc, Nijmegen, Netherlands; VU University Medical Center, Amsterdam, Netherlands; Institute for Medical Technology Assessment Erasmus University Rotterdam, Rotterdam, Netherlands; Oncological Center Isala, Zwolle, Netherlands; Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands; University of Groningen, University Medical Center Groningen, Department of Medical Oncology, Groningen, Netherlands; Leiden University Medical Center, Leiden, Netherlands; MST, Enschede, Netherlands; Medical Center Leeuwarden, Leeuwarden, Netherlands; UMCU, Utrecht, Netherlands; Amphia Hospital, Department of Medical Oncology, Breda, Netherlands; Departments of Medical Oncology and Radiology & Nuclear Medicine, Erasmus University Medical Center, Rotterdam, Netherlands; The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

**Background:** Over the past decade opportunities for surgical treatment in metastatic melanoma patients have re-emerged due to the development of novel systemic therapies. However, selecting patients who will benefit from surgery after systemic therapy is still difficult. The aim of this study is to present data on outcomes of surgery in patients with unresectable stage III and IV melanoma, who have previously been treated with immune checkpoint inhibitors (ICI) or targeted therapy, to provide insight in which patients may benefit from surgery. **Methods:** Data was extracted from the prospectively collected, nationwide, Dutch Melanoma Treatment Registry (DMTR) onunresectable stage IIIC or advanced/metastatic stage IV melanomapatients who obtained disease control with systemic therapy and underwent subsequent surgery. Disease control was defined as a complete response (CR), partial response (PR) or stable disease (SD). After disease control was achieved with systemic therapy, progressive disease (PD) was allowed as a most recent status of disease prior to surgery, to avoid excluding patients with oligoprogression. Major exclusion criteria were non-cutaneous melanoma and brain metastases. **Results:** Of 3959 patients in the DMTR database, 154 patients met our inclusion criteria. Of these patients, 79 (51%) were treated with ICI, 61 (40%) with targeted therapy and 9.1% with study or other treatments before surgery. The best response to systemic therapy was a CR in 5.2%, PR in 46.1% and SD in 44.2% of patients. At a median follow-up of 10.0 months (IQR 4-22) after surgery, the median overall survival (OS) had not been reached in our cohort and median progression free survival (PFS) was 9.0 months (95% CI 6.3-11.7). A multivariate cox regression analysis showed that when surgery led to CR or PR, the PFS and OS were better than if surgery led to SD or PD ($p < 001$). Also, ICI seemed to be more favorable than targeted therapy in both PFS (median of 15 versus 7 months) and OS (median not reached versus 32 months) ($p = 0.026$ and $p = 0.003$). **Conclusions:** We conclude that selected unresectable stage IIIC or stage IV melanoma patients might benefit from surgery after achieving disease control with systemic therapy. Expected residual tumor after surgery could be an important selection criterion. Especially patients undergoing surgery after initial tumor response on ICI have a chance of long-term survival. Research Sponsor: None.

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**10033** **Poster Session (Board #382), Fri, 8:00 AM-11:00 AM**

# Health-related quality of life (HRQL) in patients with advanced cutaneous squamous cell carcinoma (CSCC) treated with cemiplimab: Post hoc exploratory analyses of a phase II clinical trial.

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**Background:** Cemiplimab-rwlc (cemiplimab), a PD-1 Inhibitor, showed a robust clinical response in patients (pts) with metastatic (mCSCC) or locally advanced (laCSCC) CSCC not eligible for curative surgery/radiation. This post hoc exploratory analysis examined data from the EORTC cancer specific 30-item HRQL questionnaire (QLQ-C30) for pts participating in a cemiplimab phase 2 clinical trial (clinicaltrials.gov NCT02760498). **Methods:** Adults (N = 193) with invasive CSCC, ≥1 lesion and ECOG performance status ≤1 received IV cemiplimab 3mg/kg q2w (mCSCC n = 59; laCSCC n = 78) or 350mg q3w (mCSCC n = 56). At baseline (BL) and day 1 of each treatment cycle, pts were administered the QLQ-C30. Mixed effects repeated measures (MMRM) models were used to estimate mean change from BL to cycle 5 (C5) for domains/items of the QLQ-C30. For pts with data from BL to C5, the proportion who reported clinically meaningful improvement or worsening (≥10 points) or maintenance (those who did not have ≥10 point change) on each domain was determined for combined and individual treatment groups. **Results:** BL scores indicated moderate to high levels of functioning and low symptom burden. From BL to C5, a clinically meaningful improvement in pain score was observed (least squares [LS] mean [standard error] change -12.1 [2.1]; $P < .0001$); other domains/items remained stable or showed a trend towards improvement (LS mean changes < 10 points). By C5, the majority of pts experienced clinically meaningful improvement or remained stable across key domains (Table). Similar findings were observed on individual symptoms (85%-94% for dyspnea, nausea/vomiting, diarrhea, constipation, appetite loss) and in each treatment group. **Conclusions:** Cemiplimab-treated patients achieved a clinically meaningful reduction in pain and most pts either improved or maintained their HRQL, function with low symptom burden. Clinical trial information: NCT02760498. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

**Difference from baseline at C5 on key QLQ-C30 domains (all combined groups).**

| | No. (%) of pts | | |
|---|---|---|---|
| **Domain** | **Clinically meaningful improvement** | **Stable** | **Clinically meaningful worsening** |
| **Global Health Status/QoL (n = 98)** | 41 (42) | 42 (43) | 15 (15) |
| **Physical function (n = 99)** | 21 (21) | 63 (64) | 15 (15) |
| **Role function (n = 99)** | 29 (29) | 47 (47) | 23 (23) |
| **Emotional function (n = 98)** | 30 (31) | 56 (57) | 12 (12) |
| **Social function (n = 98)** | 35 (36) | 44 (45) | 19 (19) |
| **Fatigue (n = 99)** | 43 (43) | 31 (31) | 25 (25) |
| **Pain (n = 99)** | 43 (43) | 42 (42) | 14 (14) |
| **Insomnia (n = 98)** | 30 (31) | 56 (57) | 12 (12) |

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**10034** **Poster Session (Board #383), Fri, 8:00 AM-11:00 AM**

## Effect of first-line spartalizumab + dabrafenib + trametinib on immunosuppressive features detected in peripheral blood and clinical outcome in patients (pts) with advanced BRAF V600–mutant melanoma.

*Reinhard Dummer, Kelly Biette, Daniel Gusenleitner, Radha Ramesh, Celeste Lebbe, Victoria Atkinson, Mario Mandalà, Paul D. Nathan, Ana Arance, Erika Richtig, Naoya Yamazaki, Caroline Robert, Dirk Schadendorf, Hussein Abdul-Hassan Tawbi, Paolo Antonio Ascierto, Antoni Ribas, Keith Flaherty, Eduard Gasal, Jan C. Brase, Georgina V. Long; University Hospital Zürich Skin Cancer Center, Zürich, Switzerland; Novartis Institutes for Biomedical Research, Inc, Cambridge, MA; Oncology Precision Medicine, Novartis, Cambridge, MA; APHP Dermatology and CIC, U976, Université de Paris, Paris, France; Greenslopes Private Hospital, Gallipoli Medical Research Foundation, University of Queensland, Greenslopes, QLD, Australia; Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; Mount Vernon Cancer Centre, Northwood, United Kingdom; Hospital Clinic of Barcelona, Barcelona, Spain; Medical University of Graz, Graz, Austria; National Cancer Center Hospital, Tokyo, Japan; Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; The University of Texas MD Anderson Cancer Center, Houston, TX; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; University of California, Los Angeles, CA; Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia*

**Background:** Spartalizumab + dabrafenib + trametinib has previously shown a high response rate of 78% (28 of 36 pts), with a complete response (CR) rate of 42%. A correlative analysis of gene expression signatures (GES)/pathways using whole-transcriptome RNA-seq data from tissue showed that pts with a CR had significantly lower expression levels of immunosuppressive factors in the tumor microenvironment (TME) at baseline (BL). Here we analyze BL peripheral blood markers in the same cohort of pts to assess whether liquid markers can also predict response and clinical outcome to spartalizumab + dabrafenib + trametinib. **Methods:** The Phase III COMBI-i study (NCT02967692) is evaluating spartalizumab + dabrafenib + trametinib in pts with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma. In parts 1 (safety run-in; n = 9) and 2 (biomarker cohort; n = 27), blood and tissue samples were collected at BL, on treatment after 2-3 wk and 8-12 wk, and at disease progression. Lactate dehydrogenase (LDH) and other blood-based markers (including cytokine profiling [n = 45] and blood RNA-seq [114 signatures]) were assessed in all 36 pts. Pts were divided into 2 groups of 24 and 12 pts based on progression-free survival (PFS) of $>$ 1 or $<$ 1 y. **Results:** In addition to LDH, previously described blood markers such as neutrophil to lymphocyte ratio (NLR) and plasma IL-8 were identified among other neutrophil and immunosuppressive features as top candidates associated with PFS $>$ 1 y. Low plasma IL-8 levels were also associated with CR, and multivariate models suggested that IL-8 may add independent predictive value to LDH and NLR for PFS $>$ 1 y and CR. Pts with high IL-8 levels in the circulation were characterized by high neutrophil chemokine signaling ($\rho$ = 0.553) and high neutrophil markers ($\rho$ = 0.466) in the tumor as measured by RNA-seq GES levels. We observed a decrease in plasma IL-8 levels from BL upon treatment with spartalizumab + dabrafenib + trametinib. **Conclusions:** Our peripheral blood marker analysis confirmed recent findings from tissue samples that intratumoral immunosuppressive features may preclude a CR and are associated with poor outcomes. High BL plasma IL-8 levels may be associated with an immunosuppressive TME. Further validation is warranted; the randomized placebo-controlled part 3 of COMBI-i is ongoing. Clinical trial information: NCT02967692. Research Sponsor: Novartis Pharmaceuticals Corporation.

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**10035** **Poster Session (Board #384), Fri, 8:00 AM-11:00 AM**

## Phase I trial of autologous cMET-directed CAR-t cells administered intravenously in patients with melanoma & breast carcinoma.

*Payal D Shah, Alexander Chan Chi Huang, Xiaowei Xu, Paul J. Zhang, Robert Orlowski, Tina Matlawski, Joanne Shea, Amanda Cervini, Ravi K. Amaravadi, Julia C. Tchou, Lynn Mara Schuchter, E. John Wherry, Gerald P. Linette, Rosemarie Mick, Irina Kulikovskaya, Simon F. Lacey, Gabriela Plesa, Carl H. June, Robert H. Vonderheide, Tara C. Mitchell; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; Center for Cellular Immunotherapies, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; Center for Cellular Immunotherapies, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

**Background:** Advanced relapsed/refractory melanoma and metastatic triple-negative breast cancer are lethal diseases for which effective therapies are limited. We conducted a pilot phase I clinical trial (NCT03060356) to establish the safety and feasibility of intravenous autologous chimeric antigen receptor (CAR) T cell immunotherapy targeting cMET, a cell-surface antigen that is highly expressed in these cancers. **Methods:** Subjects had metastatic or unresectable melanoma (Mel) or triple-negative breast cancer (BC) with ≥30% expression of cMET on archival tissue or screening biopsy. Eligible subjects had measurable disease and progression on at least 1 prior therapy. Patients (pts) received up to 6 doses ($1x10^8$ total T-cells per dose) of RNA electroporated anti-cMET CAR T cells over a 2-week period without antecedent lymphodepleting chemotherapy. Subjects underwent pre- and post-infusion biopsies. The primary objective was to determine feasibility and safety of treatment. **Results:** 77 subjects (39 mel, 38 BC) were prescreened for tumor cMET expression and 37 (17 mel, 20 BC) met the eligibility threshold. Seven pts (4 BC, 3 Mel) received cMET-directed CAR T infusions on study. Mean age was 50 years (35-64); median (M) ECOG 0 (0-1); M prior lines of chemotherapy/immunotherapy were 4/0 for BC pts and 1/3 for Mel pts. 6 of 7 pts received all planned CAR T cell infusions, and 1 received 5 infusions. 5 pts experienced grade (G) 1 or G 2 toxicity that was possibly or definitely related to study. Toxicities occurring in ≥1 pt included: anemia (n = 3), fatigue (n = 2), and malaise (n = 2). No G ≥3 toxicities or cytokine release syndrome were observed. No pts discontinued therapy due to toxicity. Best response was stable disease in 4 pts (2 BC, 2 Mel) and PD in 3 pts (2 BC, 1 Mel). Messenger RNA signals corresponding to CAR T cells were detected by RT-PCR in the peripheral blood of all pts during the infusion period and in 2 pts after the infusion period. 6 pts underwent baseline biopsy and 4 pts underwent post-infusion biopsy. Immunohistochemical stains of CD3, CD4, CD8, CD163, L26, PD1, PDL1, Foxp3, Ki67, Granzyme B and Phospho-S6 were performed on pre- and post-treatment tissue biopsies and are being evaluated. **Conclusions:** Intravenous administration of RNA-electroporated cMET-directed CAR T cells was safe and feasible. Future directions include examination of this target using a lentiviral construct in combination with lymphodepleting chemotherapy. Clinical trial information: NCT03060356. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

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**10036** **Poster Session (Board #385), Fri, 8:00 AM-11:00 AM**

## A phase II study of ERK inhibition by ulixertinib (BVD-523) in metastatic uveal melanoma.

*Elizabeth Iannotti Buchbinder, Justine Vanessa Cohen, Rizwan Haq, F. Stephen Hodi, Donald P. Lawrence, Anita Giobbie-Hurder, Deb Knoerzer, Ryan J. Sullivan; Beth Israel Deaconess Medical Center, Boston, MA; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA; BioMed Valley Discoveries, Kansas City, MO*

**Background:** Uveal melanoma is a rare and aggressive subset of melanoma that is minimally responsive to traditional therapies. Greater than 80% of uveal melanomas have a mutation in GNAQ or GNA11 which lead to downstream signaling through the MAPK pathway. This has led to efforts to treat uveal melanoma with MEK inhibition with mixed results. Ulixertinib (BVD-523) is a potent and reversible small molecule ATP-competitive inhibitor of both ERK1 and ERK2 protein kinases which has undergone phase I testing. **Methods:** We performed a phase II study to determine the efficacy and safety of BVD-523 in patients with metastatic uveal melanoma. This was conducted as a Simon two-stage design with a total sample size of 25 patients (pts) and an initial evaluation of efficacy after 13 pts. Two responses were required to continue to the second stage. **Results:** From April 2018 to April 2019 thirteen pts were enrolled. Pts were predominantly female (69%) with a median age of 64 yrs. (34 -76). Sites of metastasis included liver (84.6%) and lung (30.8%). Grade 3 and 4 toxicities associated with therapy were consistent with BVD-523 and other ERK inhibitors and included LFT elevation, hyponatremia, pruritis, amylase elevation, anemia and rash. The best response, per RECIST 1.1, was stable disease (SD) in 4 pts, and disease progression (PD) in 7 patients. Two patients were unevaluable for response due to withdrawing themselves from the study. Median time to progression was 2.0 months (90% CI: 1.8 – 3.6 mos.). There were eight deaths due to disease progression with a median survival time of 6.9 months (90%CI: 3.2 to 8.3 mos.). Analysis of correlative data from pre- and on-treatment biopsies exploring the change in expression of key signaling proteins relating to treatment is underway. **Conclusions:** ERK inhibition with ulixertinib (BVD-523) did not demonstrate activity in patients with metastatic uveal melanoma. The toxicities observed on study were consistent with what would be expected with MAPK pathway inhibition. Clinical trial information: NCT03417739. Research Sponsor: BioMed Valley Discoveries, Inc.

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**10037** **Poster Session (Board #386), Fri, 8:00 AM-11:00 AM**

## A proteomic biomarker discovery platform for predicting clinical benefit of immunotherapy in advanced melanoma.

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**Background:** Immune checkpoint inhibitor-based immunotherapies that target CTLA-4 and the PD-1/PD-L1 axis have revolutionized the treatment of advanced melanoma due to their remarkable clinical benefit. However, only a limited number of patients respond to treatment. Therefore, biomarkers to identify appropriate candidates who will benefit from such therapy are needed. Our previous studies have identified therapy-induced, host-mediated mechanisms that drive resistance to a variety of cancer treatment modalities. Here, we explored whether assessing the systemic host-mediated response to immunotherapy can serve as a basis for predicting clinical outcome in melanoma patients. **Methods:** The cohort consisted of 34 advanced melanoma patients receiving anti-PD-1 monotherapy or anti-PD-1 and anti-CTLA-4 combination therapy. Clinical benefit was assessed. Plasma samples were obtained from patients at baseline and 2-4 weeks after a single treatment. Proteomic profiling of plasma samples was performed using ELISA-based protein arrays. A generalized linear model (GLM) was applied to a subset of the cohort (n = 13) to identify a proteomic signature that can predict clinical response to treatment. The predictive signature was then tested on the entire cohort (n = 33), excluding one patient with stable disease. **Results:** We identified a 10-protein signature that accurately distinguishes between responders and non-responders with an area under the curve (AUC) of 0.84 (confidence interval: 0.69-0.99, p-value 5.56E-04), and sensitivity and specificity of 0.94 and 0.79, respectively. These results are currently being validated in a larger cohort in an ongoing prospective study (PROPHETIC trial, NCT04056247). To explore the biological basis of resistance to immunotherapy, we performed a pathway enrichment analysis. Multiple mechanisms of resistance were identified in the non-responder group, including signaling pathways associated with immunosuppression and inflammation. Comparison between the two treatment modalities revealed pathways unique to each treatment, implying important differences between the two regimens. **Conclusions:** Our study provides insights into mechanisms of resistance to immunotherapy and paves the way towards the discovery of novel predictive biomarkers for patient stratification in melanoma. Research Sponsor: OncoHost.

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**10038** **Poster Session (Board #387), Fri, 8:00 AM-11:00 AM**

## Spatial proximity of CD8 T cells to tumor cells as an independent biomarker for response to anti-PD-1 therapy.

*Maarten Slagter, Elisa A. Rozeman, Huiwen Ding, Judith M. Versluis, Mesele Valenti, Dennis Peters, Annegien Broeks, Charlotte van Rooijen, Hugo Horlings, John B. A. G. Haanen, Erik Hooijberg, Lodewyk F. A. Wessels, Christian U. Blank, Ton N. Schumacher; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Pathology, The Netherlands Cancer Institute, Amsterdam, Netherlands; Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands; Department of Molecular Carcinogenesis, Netherlands Cancer Institute, Amsterdam, Netherlands*

**Background:** Only a subset of advanced melanoma patients respond to anti-PD-1 (aPD1) monotherapy. Upfront identification of (non-)responsiveness would help guide first-line treatment decisions, prevent overtreatment and unnecessary risk for toxicities. T cell density and expression of T cell related genes have been associated with response to aPD1, but are imperfect predictors. We investigated whether spatial proximity of CD8 T cells to tumor cells improves upon the predictive value of T cell density alone. **Methods:** Pretreatment tumor specimens from melanoma patients treated with aPD1 in the Netherlands Cancer Institute were stained for DAPI, SOX10/Melan-A, CD4, CD8, FOXP3 and PD-1 by multiplex immunofluorescence. Sections were imaged on Vectra and analyzed using HALO to optimize marker thresholds and demarcate tumor and stroma. T cell proximity to tumor cells was evaluated as difference in area under the curve between i) a spatial G-function quantifying T cell density around tumor cells in tumor areas and ii) analogous null distributions obtained by random permutation of cell labels. This assessment of co-clustering is independent of cell density and heterogeneity therein and does not reflect repulsion of T cells to stromal/marginal areas. Clinical characteristics, RECIST response and survival were collected from patient records. Associations between T cell density, T cell proximity to Sox10/Melan-$A^+$ tumor cells, other clinical biomarkers (LDH, M stage and WHO performance status) and response were examined in a Bayesian hierarchical logistic regression. **Results:** Tumor specimens of 98 patients were included, of whom 45 were treated with aPD1 as first-line therapy and 33 had an objective response. CD8 T cell proximity to tumor cells was associated with response in an independent, comparatively strong, and tissue dependent manner (cutaneous tissue: 2.78 [2.45, 3.17], visceral: 2.30 [1.95, 2.72], lymphoid: 2.12 [1.88, 2.40], format: maximal posteriori odds ratio [89% equal-tailed credibility interval]), in a multivariate model correcting for CD8 T cell density (1.74 [1.62, 1.88]), LDH (1.93 [1.72, 2.16]), M stage (0.92 [0.87, 0.98]) and WHO performance status (0.79 [0.72, 0.88]). Our model achieved an area under the ROC curve of 77.7%, whereas an analogous model omitting the proximity variable achieved 73.1%. **Conclusions:** Our analyses show that spatial proximity of CD8 T cells to tumor cells functions as an independent biomarker for response to aPD1 and suggests that preexisting CD8 T cell tumor reactivity is reflected by this spatial proximity. Research Sponsor: None.

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**10039** **Poster Session (Board #388), Fri, 8:00 AM-11:00 AM**

# Association of prior immune checkpoint blockade (ICB) with longer progression-free survival (PFS) in patients treated with intermittent versus continuous dabrafenib and trametinib: A post-hoc analysis of S1320.

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**Background:** S1320 is a phase 2 randomized clinical trial presented at the 2020 AACR Annual Meeting in April demonstrating that continuous dosing of dabrafenib and trametinib yields longer PFS than intermittent dosing of these agents in patients with $BRAF^{V600E/K}$ melanoma. Here we look at the association between prior exposure to ICB and PFS in patients randomized to either intermittent or continuous dosing on S1320. **Methods:** Patients without disease progression after 8 weeks of dabrafenib and trametinib were randomized 1:1 to proceed with intermittent therapy (3-week-off, 5-week-on) or to stay on the continuous daily dosing schedule. The design called for 206 randomized patients with the primary outcome of PFS. Response assessments were made using RECIST v1.1 at 8-week intervals. A post-hoc analysis assessed differences in PFS in the pool of all randomized patients based on prior exposure to anti-PD1 antibodies, a randomization stratification factor. Kaplan-Meier estimates and multivariable Cox regression models (controlling for pre-randomization age, Zubrod performance status, LDH, unknown primary, M-Stage) were used to evaluate the association between this stratification factor and PFS. **Results:** Of 242 patients treated on study, 105 were randomized to continuous dosing, 101 to intermittent dosing, and 36 were not randomized due to disease progression at 8 weeks or other factors. 37% of the 242 enrolled and 37% of the 206 randomized patients had previously been treated with ICB. Among all randomized patients, there were no differences in baseline characteristics comparing patients with and without prior immune checkpoint inhibitor exposure: age median 62 vs 59, LDH elevation 37% vs 39%,, stage IVB/C 73% vs 64%, Zubrod performance status 0, 57% vs 58%. PFS was longer in patients with prior ICB exposure (hazard ratio = 0.60, 95% confidence interval 0.41,-0.98, median = 6 vs 9 months from randomization, 8 vs 11 months from starting treatment). There was no difference in the association between prior ICB exposure and PFS between arms (interaction p-value = 0.62). **Conclusions:** In patients without early progression on dabrafenib and trametinib, PFS was longer with prior to exposure to ICB . Although the groups had similar baseline characteristics and rates of randomization, these results could still be influenced by non-controlled factors influencing clinicians' decisions to start a patient on immune versus targeted therapy. Clinical trial information: NCT02196181. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

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**10040** **Poster Session (Board #389), Fri, 8:00 AM-11:00 AM**

## A phase II study of vorolanib (CM082) in combination with toripalimab (JS001) in patients with advanced mucosal melanoma.

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**Background:** Vorolanib (CM082) is a multi-target tyrosine kinase inhibitor including VEGF, PDGF, c-kit, and Flt-3. Toripalimab (JS001) is a humanized IgG4 mAb against programmed death-1 (PD-1) with clinical activity in metastasis melanoma but not in its mucosal subtype. In this phase II study (NCT03602547), we investigated the safety and efficacy of CM082 in combination with JS001 in patients (pts) with advanced mucosal melanoma. **Methods:** The study enrolled pts from 18 to 75 years-old with histologically confirmed metastatic mucosal melanoma, ECOG PS 0-1, no prior systemic anticancer treatment. Eligible pts were treated with CM082 tablet (150 or 200 mg once daily) combined with JS001 (240mg every 2 weeks, IV, Q2W) until confirmed disease progression or unacceptable toxicity. Clinical response was evaluated every 8 week. The primary endpoint was overall response rate (ORR) using RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of remission (DOR), and time to first remission (TTR) according to RECIST v1.1 and iRECIST. The safety was also assessed. **Results:** Between July 2018 and April 12, 2019, 40 pts (19 pts in 150mg group; 21 pts in 200mg group) were enrolled and 38 pts were evaluable for tumor response (150mg n = 18, 200mg n = 20), with 4 (22.2%) confirmed partial response (PR), 6 (33.3%) stable disease (SD) and 8 (44.4%) progression disease (PD) in the 150mg CM082 group; 3 (15%) PRs (including 2 unconfirmed), 10 (50%) SD, and 7 (35%) PD were reported in the 200mg CM082 group. Tumors shrank in 10 pts (56%) in the 150mg group and 10 pts (50%) in the 200mg group. At data cut-off (November 28, 2019), 29 pts had PFS events (150mg n = 12; 200mg n = 17). The median PFS was 5.7 (95% CI 2.0, NE) months and 5.6 (1.9, 7.7) months in the two groups, respectively. The most common treatment-related adverse events (AEs) were grade 1 or 2, including leukopenia, elevated LDH, increased ALT, neutropenia, increased AST, and elevated GGT. Common grade 3 or higher adverse events ( $>$ 10%) were increased ALT (12 pts, 30%), increased AST (11 pts, 27.5%), neutropenia (6 pts, 15%) and elevated GGT (6 pts, 15%). Eight pts had 9 serious AEs (SAEs). The study is still ongoing and more data will be presented in the future. **Conclusions:** PFS benefit was observed in both 150mg and 200mg subgroups. This study demonstrated potentially improved efficacy with predictable toxicities of CM082 in combination with JS001 therapy, which may be an effective treatment option for pts with advanced mucosal melanoma. Clinical trial information: NCT03602547. Research Sponsor: Betta Pharmaceuticals Co.,Ltd.

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**10041** **Poster Session (Board #390), Fri, 8:00 AM-11:00 AM**

## FDG-PET metabolic tumor volume in advanced melanoma treated with ipilimumab and nivolumab (ipi/nivo).

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**Background:** Predictors of outcomes of immune checkpoint inhibitors (ICI) are desirable. We aim to investigate the prognostic value of $^{18}$F-fluorodeoxyglucose-PET/CT (FDG-PET) parameters at baseline and response monitoring of patients (pts) with advanced melanoma receiving ipi/nivo. **Methods:** From 2016-2019, melanoma pts who received ipi/nivo and had PET Response Criteria In Solid Tumors (PERCIST) measurable lesions on baseline FDG-PET were included. Baseline whole-body metabolic tumor volume (wbMTV), tumor stage, mutational status, ECOG performance score, lactate dehydrogenase (LDH) and treatment-line were correlated with overall survival (OS) in univariate and multivariate Cox-regression analysis. Response were assessed for a subset of pts with post-treatment FDG-PET based on PERCIST. **Results:** Of 162 pts receiving ipi/nivo, 122 pts (median age: 61; male: 73%; ECOG 0: 78%; raised LDH: 52%; M1c: 39%, M1d: 45% and BRAF$^{V600E/K}$mutation: 45%) met eligibility criteria. Forty percent received ipi/nivo as first-line treatment, 48% as second-line (25% post BRAF inhibitor(i)/MEKi and 23% post single-agent ICI) and 12% as third-line. At median follow-up of 21 months (mths), median OS was 20 mths (95% CI 11-not reached[NR]). Pts with above the median wbMTV had shorter OS than those with below the median wbMTV (NR vs 10 mths, 95% CI 8-NR; HR 2.0, 95% CI 1.2-3.4, p = 0.009). In multivariate analysis, wbMTV, ECOG and treatment-line were independently associated with OS. In 106 pts with post-treatment FDG-PET, 24 mths OS rate was higher for those with objective response (OR): 91% (95% CI 82-100%) vs stable disease:55% (27-100%) vs progressive disease:17% (8-35%) as best response, $p < 0.001$. OR was higher in first-line compared to second or third-line treatment, 75% vs 29-33% vs 23%, respectively, p = 0.0012. **Conclusions:** Increased baseline FDG-PET wbMTV is an independent prognostic biomarker in pts with advanced melanoma receiving ipi/nivo. FDG-PET response accurately predicts outcome. Research Sponsor: Peter MacCallum Cancer Centre Foundation.

| | | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| **Variable** | | **HR (95% CI)** | **P** | **HR (95% CI)** | **P** |
| **wbMTV** | Higher median vs lower median | 2.0 (1.2, 3.4) | 0.009 | 2.0 (1.1, 3.6) | 0.015 |
| **LDH** | > 1xUNL vs NL | 1.3 (0.7-2.5) | 0.4 | | |
| | > 2xUNL vs NL | 1.7 (0.7-4.0) | | | |
| **ECOG** | 1/2 vs 0 | 3.4 (2-5.9) | < 0.0001 | 3.2 (1.7-6.3) | 0.0005 |
| **Stage** | M1d vs IIIC/M1a/M1b/M1c | 1.8 (1.1-3.1) | 0.02 | 1.37 (0.7-2.6) | 0.3 |
| **Mutation** | NRAS vs BRAF | 0.5 (0.3-1.0) | 0.07 | 4.3 (1.1-17.2) | 0.1 |
| | WT vs BRAF | 0.6 (0.3-1.1) | | 4.0 (1.0-15.3) | |
| **Treatment-line** | 2nd post BRAFi/MEKi vs 1st | 4.4 (2.1-8.9) | 0.0006 | 13.8 (3.3-58) | 0.0008 |
| | 2nd post ICI vs 1st | 2.8 (1.3-5.9) | | 4.1 (1.8-9.6) | |
| | 3rd vs 1st | 3.5 (1.5-8.1) | | 9.9 (2.2-44.3) | |

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**10042** **Poster Session (Board #391), Fri, 8:00 AM-11:00 AM**

## Real-world outcomes of advanced melanoma patients not represented in phase III trials.

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**Background:** A large proportion of patients with advanced melanoma is not represented in phase III clinical trials, due to ineligibility. Real-world efficacy evidence of immune- and targeted therapies in these patients is lacking. We aimed to provide insight in survival outcomes of systemically treated patients who were not represented in the phase III trials in order to support clinical decision-making. **Methods:** Systemically treated ineligible patients with advanced melanoma diagnosed between 2014-2017 were analyzed. Prognostic importance of factors associated with overall survival (OS) was assessed by Kaplan Meier method, Cox regression models, predicted OS probabilities of prognostic subgroups and a conditional inference survival (decision) tree. **Results:** Of 2,536 systemically treated patients with advanced melanoma, 1,004 (40%) patients were ineligible for phase IIII trials. Ineligible patients had a poorer median OS (mOS) compared to eligible patients (8.8 vs 23 months). Eligibility criteria most strongly correlated with survival in ineligible systemically treated patients with ECOG Performance Score (PS) $\geq$2 vs PS 0-1 (HR 1.95 (95%CI: 1.52-2.5)), symptomatic brain metastases (BM) vs absent BM (HR 1.71 (95%CI: 1.34-2.18)) and LDH $>$ 500 U/l vs normal (HR 1.89 (95%CI: 1.49-2.41)). All other factors for ineligibility were not associated with OS. By combining ECOG PS, BM and LDH, 18 subgroups were created. The 3-year survival probability of patients with ECOG PS $\leq$1, asymptomatic BM and normal LDH was 35.1%. Patients with ECOG PS of $\geq$2 with or without symptomatic BM had a mOS of 6.5 and 11.3 months and a 3-year survival probability of 9.3% and 23.6% respectively. In the decision tree, the covariate with the strongest predictive distinctive character for survival was LDH, followed by ECOG PS. Prognosis of LDH of $>$ 500 U/L is infaust, although still long-term survival is possible (3-year survival probability of 15.3%). The decision tree showed the prognosis of patients with symptomatic BM can be good if ECOG PS is 0 and patients are aged $\leq$55 years (mOS of 22.3 months). **Conclusions:** Patients with advanced melanoma not represented in phase III trials treated with systemic therapy can achieve long term survival. LDH was the strongest predictive factor associated with survival, followed by ECOG PS and symptomatic BM. Other factors for ineligibility were not associated with OS. These results, together with the decision tree, can be used to provide insight in outcomes to facilitate the shared decision-making process when comparative studies are not available. Research Sponsor: None.

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**10043** **Poster Session (Board #392), Fri, 8:00 AM-11:00 AM**

# Estimating treatment-free survival (TFS) over extended follow-up in patients (pts) with advanced melanoma (MEL) treated with immune-checkpoint inhibitors (ICIs): Five-year follow-up of CheckMate 067.

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**Background:** We previously defined a novel outcome, TFS, to characterize the time between ICI therapy cessation and subsequent therapy initiation/death. TFS is part of an integrated analysis to comprehensively describe how pts spend overall survival (OS) time, on and off treatment, with/without treatment-related toxicity. We reported survival states, including TFS, in ICI-treated pts with MEL in the phase 3 CheckMate 067 trial (NCT01844505) over the 36-mo period since randomization (Regan. *J Clin Oncol.* 2019); 60-mo results are presented here. **Methods:** Data were analyzed for 937 pts with MEL who started treatment with nivolumab (NIVO) plus ipilimumab (IPI), NIVO, or IPI in CheckMate 067. TFS was defined as the area between the Kaplan–Meier (KM) curves for 2 conventional time-to-event endpoints defined from randomization: time to protocol therapy cessation and time to subsequent therapy/death. TFS was also divided into TFS with/without grade ≥3 treatment-related adverse events (TRAEs), and OS was estimated. The area under each KM curve was estimated by the 60-mo restricted mean (r-mean) time to event and expressed as a percentage of the 60-mo period. Bootstrapped 95% CIs were calculated for differences. **Results:** Over the 60-mo period, pts spent an average of 33%, 17%, and 20% of time free of treatment after receiving NIVO+IPI, NIVO, and IPI, respectively (r-mean TFS, 19.7, 9.9, and 11.9 mo; Table). NIVO+IPI-treated pts had r-mean TFS that was 9.8 mo longer than NIVO-treated pts (95% CI, 6.7–12.8) and 7.8 mo longer than IPI-treated pts (95% CI, 4.6–11.0). Mean TFS with grade ≥3 TRAEs remained a small proportion of the 60-mo period at 3%, 2%, and < 1% with NIVO+IPI, NIVO, and IPI, respectively. **Conclusions:** With extended follow-up, average TFS with/without toxicity represented greater percentages of the 60-mo vs 36-mo period for NIVO+IPI and NIVO, but not for IPI. Pts treated with NIVO+IPI continued to have TFS twice as long as those treated with NIVO alone, due to earlier therapy cessation for toxicity without disease progression and subsequent resolution of many of those toxicities. The majority of TFS time was spent without grade ≥3 TRAEs across all arms. Research Sponsor: Bristol-Myers Squibb.

**Estimated r-mean TFS time and survival states over 60-mo follow-up.**

| | r-mean time (mo) | | |
|---|---|---|---|
| **Survival state** | **NIVO+IPI** | **NIVO** | **IPI** |
| **Time on protocol therapy** | 12.3 | 16.9 | 2.6 |
| **TFS** | 19.7 | 9.9 | 11.9 |
| **TFS without grade ≥3 TRAEs** | 18.1 | 9.0 | 11.7 |
| **TFS with grade ≥3 TRAEs** | 1.6 | 0.9 | 0.2 |
| **Survival after subsequent therapy initiation** | 6.6 | 9.3 | 13.9 |
| **OS** | 38.6 | 36.1 | 28.4 |

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**10044** **Poster Session (Board #393), Fri, 8:00 AM-11:00 AM**

## CA209-9JC: A phase II study of first-line nivolumab (NIVO) in patients (pts) with locally advanced or metastatic cutaneous squamous cell carcinoma.

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**Background:** Cutaneous squamous cell carcinoma (cSCC) is among the most frequent malignancies worldwide, and an increasing incidence has been documented over the past decades. For those not amenable to treatment with curative intent, immune checkpoint blockade (ICP) with anti-PD-1 monoclonal antibodies emerged as a novel therapeutic option, supported by evidences of high mutational burden and expression of PD-L1. In this single-arm study, we sought in investigate the activity of NIVO in pts with advanced cSCC (AcSCC). **Methods:** We conducted a Simon two-stage, open-label, phase II study to evaluate the safety/efficacy of NIVO for up to 24 systemic-treatment-naïve pts with metastatic and/or locaally advanced cSCC. NIVO at 3mg/kg was administered intravenously every 2 weeks (w) until disease progression, unacceptable toxicity or 12 months of treatment. The primary endpoint was the best objective response rate (bORR) at 24w as per RECIST criteria. Tumor measurements were performed every 12w. Secondary endpoints included safety/tolerability, progression-free survival (PFS) and overall survival (OS). **Results:** Between October 2018 and October 2019, 24 pts with AcSCC were enrolled, with a median age of 74 years (range 48-93) and a male/female ratio of 1.4:1. Most frequent primary sites were head/neck (42%), trunk (29%) and extremities (25%); identified risk factors included chronic sun exposure or burn scars in 66 % and 12.5 %, respectively. Upon enrolment, the proportions of patients with locally advanced, locoregional (regional lymph node involvement) and metastatic disease were 16.6%, 66.6% and 16.6%, respectively. At data cut off (median number of doses of NIVO: 15), 15 pts (62.5%) remain on treatment and 6 pts have progressed and/or died. Three pts completed 12 months of treatment and entered surveillance. Among 22 pts evaluable for response (n = 2 have not reached 12w of treatment), the bORR was 54.5% (12/22), and disease control (stable disease or objective response) was achieved in 77% (17/22). Median duration of response, PFS and OS have not been reached. Grade $\geq$3 treatment-related adverse events occurred in 21% of the pts, and 1 patient discontinued NIVO due to toxicities. **Conclusions:** NIVO resulted in robust antitumor activity and good tolerability in systemic treatment-naïve pts with AcSCC. There were no new safety signals, despite the inclusion of individuals at advanced ages. These data provide further evidence to support the use of ICP as the standard treatment option for pts with AcSCC. Clinical trial information: NCT03834233. Research Sponsor: BMS.

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**10045** **Poster Session (Board #394), Fri, 8:00 AM-11:00 AM**

## Response to immune checkpoint inhibitor (ICI) rechallenge after high-grade immune related adverse events (irAE) in patients (pts) with metastatic melanoma (MM).

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**Background:** ICIs have transformed MM mortality. Pts receiving ICIs may experience high-grade irAEs that limit continuation of treatment per current guidelines. We aimed to evaluate the safety and response rate of ICI rechallenge. **Methods:** 551 MM pts treated with ICI were retrospectively reviewed from Jan 2014 to Jan 2020 after IRB approval. The incidence of a recurrent irAE in pts with ICI rechallenge within the same drug class after an initial high-grade (Grade III/IV) irAE was evaluated. Age, gender, irAEs, and outcomes were descriptively analyzed within the rechallenged cohort. **Results:** 32.7% of pts (180/551) experienced a high-grade irAE. 60.0% of these (108/180) pts were on combination therapy with at least one ICI. 50.6% (91/180) of pts were rechallenged with ICI within the same drug class. The rechallenged cohort had a median age of 63.8 [range: 28-86] years and 48.4% was female. The cohort's initial irAE occurred at a median of 7.6 weeks from treatment onset with Grade 3/4 severity of 60.0% /40.0% (91). Toxicities included colitis 27.5% (25/91), hepatitis 23.1% (21/91), skin toxicity 22.0% (20/91), adrenal insufficiency 5.5% (5/91) hypophysitis 5.5% (5/91), neurological abnormality 4.4% (4/91), pancreatitis 3.3% (3/91), hematological abnormality 3.3% (3/91), arthralgia 3.3% (3/91), myalgia 3.3% (3/91), pneumonitis 2.2% (2/91), insulin dependent diabetes 1.1% (1/91), fatigue 1.1% (1/91), vasculitis 1.1% (1/91), and hyponatremia 1.1% (1/91). ICI rechallenge occurred at a median of 9.7 weeks from the first Grade 3/4 irAE. 51.8% (29/56) pts initially treated with combo were rechallenged with combo, while 48.2% (27/56) were rechallenged with single agent ICI. Of pts initially treated with single ICI, 60% (21/35) were rechallenged with single agent ICI and 40% (14/35) with combo. With a median follow-up of 21.1 months after rechallenge, irAEs occurred in 75.8% (69/91), with 44.9% of irAEs (31/69) presenting as a different type from the initial event and 31.9% (22/69) as high-grade events. There were no rechallenge irAE-related deaths. Within the rechallenge cohort, 39.6% (36/91) of pts had disease progression. Clinical benefit was achieved in 60.4% (55/91) of pts: 40.7% (37/91) complete response, 11.0% (10/91) partial response and 8.8% (8/91) stable disease. **Conclusions:** ICI rechallenge can be safely administered in pts with MM after recovery from an initial high-grade irAE. Rechallenge irAE's did not always reflect initial irAE's. Close monitoring for any type or grade of IRAE is recommended. Research Sponsor: None.

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**10046** **Poster Session (Board #395), Fri, 8:00 AM-11:00 AM**

## Discordant response comparing 18F-FDG PET/CT with response assessment by RECIST in patients with advanced melanoma treated with immune checkpoint blockade.

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**Background:** Immune checkpoint blockade (ICB) has changed the natural history advanced melanoma (AM). Based on phase III trial, which used RECIST criteria, the complete response (CR) rate with anti-PD1 therapy is around 20%. In daily practice, PET/CT is a useful tool to evaluate response to treatment in melanoma patients. Little is known about the number of patients who achieve metabolic CR by PET/CT but with anatomic residual disease and their prognosis. **Methods:** We conducted a retrospective analysis of patients with AM treated with ICB who achieved metabolic CR by PET/CT but with residual disease on tomography and compared to patients with RECIST CR in a high-volume cancer center. Progression-free (PFS) and overall survival (OS) were obtained by Kaplan Meier method and log-rank test. **Results:** One hundred seventy pts with AM treated with anti-PD1 (79%) or anti-PD1 + anti- CTLA4 (21%) betweenSeptember 2013 and December 2019 were analyzed. At a median follow-up of 23.6 months, seventy-five (44%) pts achieved CR. RECIST criteria: 22 pts (29.3%) and metabolic CR: 53 pts (70.7%). All patients with metabolic CR had RECIST partial response. The median total time on treatment was 14.8m (95%CI:0.9-42.3). The median time to reach CR was 5.4m (95%CI: 3-39). The median time of treatment after CR was 6.8m (95%CI: 0-21.4). The rate of CR patients off treatment at the moment of this analysis was 69%. The median follow-up after discontinuing treatment was 5.2m. There was no difference in PFS (36 month-rate: 84.4% vs 74%, p:0.64) and OS (36 month-rate: 100% vs 86.3%, p:0.14) between pts with CR based on RECIST or PET-CT, respectively. Median time for PFS and OS have not been reached until the date cut-off. Nine pts have relapsed (12%). Seven of them had residual disease on tomography but with no metabolic active lesion(s) at the time of the end of treatment. **Conclusions:** Twice more patients achieve complete response considering only metabolic parameters on PET/CT compared to RECIST criteria and they seem to have comparable prognosis. Research Sponsor: None.

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**10047** **Poster Session (Board #396), Fri, 8:00 AM-11:00 AM**

## A first-in-human phase I/II study of HL-085, a MEK Inhibitor, in Chinese patients with NRASm advanced melanoma.

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**Background:** MEK inhibitors have confirmed effects on malignant tumors, especially for those induced by RAS/RAF dysfunction. There is no effective drug in clinic for NRASm advanced melanoma. HL-085 is a selective MEK inhibitor, showing good safety and efficacy in preclinical studies. This study is a phase I/II study to evaluate the safety, tolerability, pharmacokinetic and preliminary anti-cancer activity of HL-085 in patients(pts) with NRASm advanced Melanoma. **Methods:** The phase I/II study is conducted using a "3+3" regimen for dose escalation. The pts are treated with HL-085 at a starting dose of 0.5mg BID to 18mg BID. Adverse events (AEs) are reported per NCI CTCAE version 5.0. Preliminary anti-cancer activity is evaluated by ORR, DCR, PFS and DoR. **Results:** Total 33 pts were enrolled in the study. The histologic types were acral (51.4%), mucosal (27.2%) and other (21.2%). The NRAS mutation types were Q61 (72.7%), G12 (18.2%) with half for G12D, and G13 (9.1% ). Most AEs were G1 or G2, and the most common drug-related AEs were rash, increased creatine phosphokinase, peripheral edema, increased alanine aminotransferase and aspartate aminotransferase. No dose-limited toxicity was observed. PK analysis was shown linear PK profile with no obvious accumulation. Among 12 evaluable pts over 9 mg, 4 pts were at the stage of M1c with 1 liver metastasis. Average targeted tumor size was 74.6mm with the largest 184 mm. 10 pts achieved tumor shrinkage [ 60% with Q61, 20% with G12D, 10% each with G12S and G13R]. 4 pts ( 2 acral, 1 mucosal and 1 other, each pt has mutaiton type of Q61R,Q61L, Q61K and G12S respectively ) had confirmed partial response(PR) [median treatment duration 26.6 weeks (wks) with longest 47.6 wks]). 6 pts achieved stable disease (SD) (median treatment duration 15.72 wks with longest 24 wks), and 66.7% were over 14 wks . The median PFS was 17.4 wks, and confirmed best ORR was 33.3% with DCR 83.3% . **Conclusions:** Our data demonstrated that HL-085 is well tolerated, with manageable side-effects and promising anti-cancer activity in pts with NRASm advanced melanoma. Clinical trial information: NCT 03973151. Research Sponsor: Shanghai KeChow Pharma.

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**10048** **Poster Session (Board #397), Fri, 8:00 AM-11:00 AM**

## Clinical outcomes with early-elective discontinuation of PD-1 inhibitors (PDi) at one year in patients (pts) with metastatic melanoma (MM).

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**Background:** Randomized trials of PDi in MM permitted treatment for 2 years (pembrolizumab) or more (nivolumab). However, the optimal treatment duration is unknown, and shorter courses may be effective. We reviewed clinical outcomes of pts who electively discontinued PDi at 1 year at our institution. **Methods:** We performed a real-world, observational cohort study of pts with MM treated with single-agent PDi from 1/1/2015 to 12/31/2018 at Huntsman Cancer Institute. This was a continuous series of pts who made the joint decision with their provider to electively discontinue PDi at 1 year ( $>$ 6 mos and $<$ 18 mos) in the setting of ongoing treatment response or disease stability. Exclusion criteria: PDi with other systemic therapy, discontinuation due to disease progression or immune-related adverse event, and PDi in neoadjuvant, adjuvant, or clinical trial settings. Local therapies, as in real-world, were allowed. Best objective response (BOR) per RECIST 1.1 at PDi discontinuation, progression-free survival (PFS) and retreatment characteristics were analyzed. **Results:** Of 485 pts who received PDi, 52 met inclusion criteria. Median age was 60.5 years and 26.9% were female. Median duration of PDi from first to last dose was 11.1 mos (95% CI 10.5 - 11.4). BOR was complete response in 13 (25%), partial response in 28 (53.8%), and stable disease in 11 (21.2%) pts. After median follow-up of 20.5 mos (range 3 - 49.2) from treatment discontinuation, 39 (75%) pts remained without disease progression (median PFS not reached). Only 13 (25%) pts progressed. Median time to progression after treatment discontinuation was 3.9 mos (range 0.7-30.9). Of the 13 pts, 7 immediately underwent successful localized treatment to the solitary site of progression (3 SRS/SBRT, 4 resection; followed by PDi in 2), 5 were retreated with PDi and 1 received BRAF/MEK followed by PDi. Retreatment with PDi controlled disease in all 5 pts. All pts except 1 were alive at data cut-off. **Conclusions:** In the largest continuous series of pts with MM who electively discontinued PDi after 1 year of treatment, the majority remained without progression on follow-up. Risk of disease progression even in pts with residual disease on imaging was low, and retreatment was effective. Strengths of our study include real-world cohort and treatment pattern analysis. Limitations include single-institution, retrospective design. After prospective validation, elective PDi discontinuation at 1 year may reduce financial and PDi-related toxicity without sacrificing outcomes. Research Sponsor: None.

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**10049** **Poster Session (Board #398), Fri, 8:00 AM-11:00 AM**

## Activity and safety of third-line BRAF-targeted therapy (TT) following first-line TT and second-line immunotherapy (IT) in advanced melanoma.

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**Background:** Patients with advanced melanoma who progress on 1st line TT and 2nd line IT have limited treatment options. We explored the safety and efficacy of re-treatment with 3rd line TT. **Methods:** was pooled from 6 centers in Australia from 2009-2018. Eligible patients with BRAF V600 mutant melanoma had 1st line therapy with a BRAF/MEK inhibitor, 2nd line IO and were re-challenged with a BRAF/MEK inhibitor. **Results:** 90 patients were included; median age 61 years, 78% BRAF V600E, 89% ECOG 0-1 at baseline. 1st line TT was combination BRAF/MEK inhibitors in 80%, predominately dabrafenib/trametinib. Response to 1st line therapy was CR 20%, PR 41%, SD 17% and PD 13% and median duration of therapy was 7.2 months (0-33 months). 70% stopped for progressive disease, 9% toxicity and 16% had a planned switch to immunotherapy. For 2nd line IT, 49% had PD-1 alone, 33% had PD-1+CTLA-4, 14% had CTLA-4 alone. Only median duration on IT was 67 days (0-23 months), 81% ceased for PD, 14% for toxicity. Of patients who had a planned switch to IO before 1st line TT progression, one patient responded to second line IO with SD as BORR, there were no other responses to 2nd line IO in the planned switch group. At 3rd line TT re-challenge, 54% were AJCC stage IVd, 34% IVc, 51% had elevated LDH, 59% ECOG 0-1. 47% were re-challenged with dabrafenib/trametinib, 33% vemurafenib/cobimetinib, 11% encorafenib/binimetinib. BORR was 28%, with median duration on 3rd line TT 81 days. The OS was 1.7 years, with 34% alive at time of analysis. **Conclusions:** Despite progression on 1st line TT and 2nd line IT, patients may experience meaningful response and on re-challenge TT. Research Sponsor: None.

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**10050** **Poster Session (Board #399), Fri, 8:00 AM-11:00 AM**

## Circulating tumor DNA (ctDNA) using Guardant360 to predict response in BRAF V600 WT metastatic melanoma (MM) patients (pts) receiving immune checkpoint inhibitors (ICI).

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**Background:** ctDNA detected by ddPCR predicts ICI response in MM, although its utility is limited to pts with known recurring mutations eg. *BRAF*, *NRAS*, *KIT*. We sought to overcome this limitation by using a next generation sequencing approach in *BRAF V600* wild type (WT) MM pts. **Methods:** Plasma was collected at baseline and Week (wk) 6 in 35 *BRAF V600* WT MM pts treated with ICI. Cell free (cf)DNA was analyzed using Guardant360 and only somatic non-synonymous and promoter variants were considered. Pts who failed cfDNA extraction at baseline were excluded (n = 3). Favorable ctDNA was defined as undetectable ctDNA at wk 6 and unfavorable ctDNA defined as detectable ctDNA at wk6. Response was according to RECIST at first restaging. **Results:** Of the evaluable 32 pts (64 plasma samples), median baseline cfDNA quantity was 33ng (range 4-657ng) and ctDNA was detected in 29/32 pts (91%). All 3 pts with undetectable baseline ctDNA had less than 10ng cfDNA compared to only 1/29 pts with detectable baseline ctDNA. Number of mutations identified in the 29 ctDNA-positive pts was 4 per pt (range 1-22). Response assessment was performed on 30 evaluable pts. Candidate driver mutation(s) in *BRAF*, *NF1*, or *N/K/HRAS* were identified in 26/30 pts. These mutations were often detected with other established mutations involved in tumorigenesis (eg. *TERT* promoter), or passenger mutations (eg. clonal hematopoiesis). Analysis of driver mutations revealed a sensitivity and specificity in predicting treatment failure of 92% and 93%, respectively (table). When all mutations identified were evaluated for treatment response, 9/18 responding pts retained some ctDNA at wk 6, although this never included *TERT* variants. The resulting sensitivity and specificity in predicting treatment failure changed to 100% and 50%, respectively, when all cfDNA variants were included. **Conclusions:** The extensive coverage of Guardant360 improves ctDNA detection in *BRAF V600* WT MM pts, allowing non-invasive, rapid, and longitudinal assessment of response in a broader population. The expanded coverage also identifies passenger variants of potential non-MM origin, eg. clonal hematopoiesis, and with significant overlap with ctDNA, it is not possible to distinguish between the two in the circulation. We therefore recommend identification and monitoring of known cancer driver mutations only. Research Sponsor: National Health and Medical Research Council.

| | Driver mutation (n = 26) | | *TERT* promoter (n = 20) | | All mutations (n = 30) | |
|---|---|---|---|---|---|---|
| | Favorable | Unfavorable | Favorable | Unfavorable | Favorable | Unfavorable |
| **PR/CR** | 13 | 1 | 10 | 0 | 9 | 9 |
| **SD/PD** | 1 | 11 | 1 | 9 | 1 | 11 |

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**10052** **Poster Session (Board #401), Fri, 8:00 AM-11:00 AM**

## Preclinical and clinical studies of a class I/IV HDAC inhibitor, mocetinostat, in melanoma.

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**Background:** Mocetinostat is a class I/IV HDAC inhibitor with HDAC1/2/3/11 activity. Preclinical murine data suggest that HDAC inhibition has immune activity and may augment the clinical benefit of checkpoint inhibition. Several trials are assessing the effects of adding HDAC inhibition to PD-1 blockade. **Methods:** Patients with therapy-naive metastatic melanoma were treated in a pilot phase Ib trial with nivolumab at 3 mg/kg/ipilimumab at 1 mg/kg every three weeks four times and a starting dose of mocetinostat at 70 mg orally three times a week in a 12-week induction cycle followed by 12-week maintenance cycles of nivolumab 240 mg every 2 weeks and mocetinostat at the same dose and schedule as induction. Endpoints were toxicity, definition of a recommended phase 2 dose and preliminary assessment of response as well as correlative marker determination. Peripheral blood mononuclear blood cells from patients were tested *in vitro* at varying concentrations of mocetinostat, and its impact on T, regulatory T and myeloid-derived suppressor cell phenotypes were assessed by flow cytometry, as well as cytokine production by Luminex. **Results:** In the mocetinostat, nivolumab and ipilimumab phase I trial, 10 patients were treated, including 5 males and 5 females with a median age of 59. There were 2 complete and 5 partial responses confirmed; 6 of 7 are maintained at a median of 16 months of follow up. Three patients had progressive disease. Seven patients had grade 3-4 immune related adverse events; in 3 they were multiple. No patients died. *In vitro*, mocetinostat at doses from 125 to 500 nM increased relative percentage of CD4/CD8 central memory T cells, and decreased IL-6 levels while increasing interferon-gamma production ($p = 0.005$). Percentages of regulatory T and monocytic myeloid-derived suppressor cells were decreased by mocetinostat ($p = 0.005$), which also down-modulated regulatory T cell function by reducing FOXP3, HELIOS and GARP ($p = 0.001$). **Conclusions:** *In vitro*, mocetinostat promoted accumulation of central memory CD8 and CD4 T cells from melanoma patients, and decreased percentages and suppressive activity of T regulatory cells and myeloid-derived suppressor cells. In a pilot clinical trial, mocetinostat combined with nivolumab and ipilimumab in treatment-naïve metastatic melanoma patients exhibited a response rate of 70% with long duration of response but all ten patients treated had at least one grade 3 or 4 immune-related toxicity. De-escalation of the mocetinostat dose to 50 mg three times a week was felt to be indicated due to the toxicity of the triple regimen. Clinical trial information: NCT03565406. Research Sponsor: Mirati Pharmaceuticals.

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**10053** **Poster Session (Board #402), Fri, 8:00 AM-11:00 AM**

## Risk of disease progression (PD) following discontinuation of BRAF±MEK targeted therapies for reasons other than PD in patients (pts) with metastatic or unresectable melanoma.

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**Background:** In pts with metastatic melanoma bearing BRAF V600E/K mutations BRAF V600±MEK inhibitors are administered until PD/unacceptable toxicity. In patients achieving durable responses, outcomes following discontinuation for reasons other than PD are largely unknown. **Methods:** We identified all patients who interrupted BRAF±MEK inhibitors for reasons other than PD after complete (CR) or partial response (PR) from a clinical dataset of patients with *BRAF* mutated metastatic/unresectable melanoma treated with targeted therapy at a single Institution. **Results:** We included 24 pts. Fifteen (62.5%) and 9 (37.5%) pts were treated respectively with BRAF inhibitor monotherapy and BRAF+MEK inhibitor combination. All pts had normal baseline LDH and ECOG PS0, 2 (8%) pts had brain metastases and 15 (62.5%) had multi-organ metastatic involvement. Dose reduction was required for 12 (50%) pts. Median treatment duration was 59 (12-88) months. Causes of discontinuation were unacceptable toxicity (19 pts-79%) and consent withdrawal (5 pts-21%). At the time of discontinuation, 17 (71%) and 7 (29%) pts had achieved respectively CR and PR. At a median follow up of 31 (8-59) months after treatment discontinuation, 9 (37.5%) pts had experienced PD. Median time to PD after treatment discontinuation was 9 (3-16) months. At time of PD, 2 (22%) pts displayed involvement of new organ sites. Risk of PD following discontinuation was respectively 31% and 45% at 12 and 24 months. Neither baseline characteristics nor treatment duration and time to best response influenced risk of PD; we found a non-significant trend towards higher risk of relapse for patients interrupting treatment with residual disease compared to those who interrupted treatment after achieving CR [HR 3.3; 95%CI (0.8–14.1); log-rank p = 0.081]. After PD, 6 pts received BRAF+MEK inhibitors with a response rate of 100% and 3/6 pts achieving CR. **Conclusions:** In a subset of patients with favorable prognostic characteristics and retained sensitivity to BRAF±MEK inhibitors, treatment discontinuation was associated with relevant risk of relapse with about one third of pts experiencing PD within one year. Biomarker studies are needed to identify pts who might safely discontinue therapy due to sustained toxicity, especially after achieving CR. Research Sponsor: None.

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**10054** **Poster Session (Board #403), Fri, 8:00 AM-11:00 AM**

## Landmark analysis of immunotherapy duration and disease free survival in advanced melanoma patients with a complete response.

*Grayce N. Selig, Alexander Chan Chi Huang, Giorgos C. Karakousis, Wei Xu, Cathy Zheng, Mary Carberry, Lydia Giles, Kristin Kreider, Suzanne McGettigan, John Nicholas Lukens, Lynn Mara Schuchter, Ravi K. Amaravadi, Tara C. Mitchell; Department of Medicine, University of Pennsylvania, Philadelphia, PA; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

**Background:** Checkpoint blockade improves survival in patients with melanoma, with durable complete responses (CR) after stopping therapy. Based on data from KEYNOTE-001, immunotherapy is often continued for 24 months in patients with confirmed CR. Outcomes with treatment of less than 24 months hav not been adequately evaluated and reported. If equally efficacious, shorter courses would potentially reduce health care costs and toxicity. **Methods:** 45 patients with locally advanced stage III and IV melanoma who received immunotherapy (pembrolizumab, nivolumab or ipilimumab/nivolumab) as 1$^{st}$ line or subsequent therapy, achieved a CR, and stopped therapy were identified under an IRB approved protocol at Penn. Disease Free Survival (DFS) was defined as time from declaration of CR until recurrence or date of analysis (1/15/20). Landmark DFS from time of CR was analyzed based on duration of therapy (less than or greater than 7 months, based on early trial requirements to treat patients with confirmed CR for at least 6 months). Rationale for stopping (toxicity or CR) was also analyzed. **Results:** Of 45 patients with CR, 27 (60%) were treated less then 7 months (median 4.8, range 1 day to 6.7 months) and 18 (40%) were treated for greater than 7 months (median 12.4, range 7.5 to 24.2 months). Patients who were treated for less than 7 months had a median DFS from time of CR of 30.4 months (95% CI 23.7 to 37.2, range 2.9 to 65.7 months). Patients treated for greater than 7 months had a median DFS of 28.0 months (95% CI 18.9 to 37, range 8.5 to 73.7 months). Patients who stopped due to toxicity (N = 17, 40%) had a median treatment duration of 3.7 months. Their median DFS from time of CR was 30.4 months (95% CI 20.7 to 40.1, range of 2.9 to 65.7 months). Patients who stopped due to CR (N = 28, 60%) had a median treatment duration of 8.5 months. Their median DFS was 27.6 months (95% CI 21.2 to 34 range 7.2 to 73.7 months). Two of 27 (7.4%) patients treated for less then 7 months and 3 out of 18 (16%) patients treated greater than 7 months recurred after stopping. One out of 17 (5.8%) recurred after stopping for toxicity vs. 4/28 (14.3%) who stopped after CR. **Conclusions:** Patients who stop therapy at less than 7 months have CRs that are equally durable as those treated longer than 7 months, without reduction in landmark DFS. Patients who stopped therapy due to toxicity and then achieved a CR had no difference in DFS compared to patients treated until CR. There was no significant difference in recurrence after achieving a complete response in patients treated for a longer vs shorter treatment course. Research Sponsor: None.

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**10057** **Poster Session (Board #406), Fri, 8:00 AM-11:00 AM**

## Long-term immune-related adverse events under PD-1 inhibitors: a multicenter prospective cohort study (MELBASE).

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**Background:** PD-1 inhibitors (anti-PD1) are frequently associated with immune-related adverse events (IRAE). Since melanoma patients included in clinical trials were frequently treated during two years, data on IRAE occurring after 2 years of treatment are lacking. This study aimed to describe IRAE in melanoma patients treated with anti-PD1 for longer than 2 years in a real-life setting. **Methods:** Patients were screened from MelBase, a French multicentric biobank dedicated to the prospective follow-up of unresectable stage III or IV melanoma. All patients who received anti-PD1 for at least 2 years between January 2013 and November 2019 were included. Among them, patients who experienced IRAE and long-term IRAE defined as IRAE occurring after 2 years of anti-PD1 were identified. **Results:** Among 1849 patients with advanced melanoma included in Melbase, 119 patients received anti-PD1 monotherapy during at least 2 years, from January 2013 to November 2019, with a median follow-up of 41.7 months (25.2-57.5). Patients characteristics at treatment initiation were: male gender (61%), mean age of 63 years old, past history of autoimmune disease (11%), BRAF WT (72%), AJCC stage IV (84%), brain metastases (22%), ECOG 0-1 (88%) and normal LDH (56%). Patients were treated with Nivolumab (n = 53) or Pembrolizumab (n = 66). IRAE occurred in 99 patients (83%) with a median time of 13.3 months (0-53.9), including severe IRAE (grade 3 or 4) in 30 patients (30%). Long-term IRAE, mostly grades 1-2, occurred in 52 patients (43%). Long-term IRAE led to 5 hospitalizations (4%) of which 4 were grades 3-4. Among patients with long-term IRAE, 45 patients (87%) previously experienced IRAE within the first 2 years of anti-PD1 and 29 patients (56%) experienced multiple IRAE. **Conclusions:** Our data demonstrate that long-term IRAE are frequent especially in patients who already experienced IRAE within the first two years of treatment. These data should be taken into account to establish formal recommendations on the duration of anti-PD1 therapy. Research Sponsor: BMS, MSD, Novartis, Roche.

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**10059** **Poster Session (Board #408), Fri, 8:00 AM-11:00 AM**

## Clinical outcomes in patients with $BRAF^{V600}$ mutant melanoma and undetectable circulating tumor DNA treated with dabrafenib and trametinib.

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**Background:** Circulating tumor DNA (ctDNA) analysis has been promoted as a less-invasive surrogate assay for tumor-tissue based tumor oncogene analysis. Here, we associate detection of BRAF mutant ctDNA with PFS and OS in patients with tissue-confirmed $BRAF^{V600}$ mutant melanoma enrolled in S1320, a randomized phase 2 clinical trial of continuous versus intermittent dosing of dabrafenib and trametinib. **Methods:** Patients with $BRAF^{V600}$ melanoma received continuous therapy with dabrafenib and trametinib for 8 weeks after which patients were randomized 1:1 to proceed with intermittent treatment on a 3-week-off, 5-week-on schedule or to continue with continuous therapy. Pre-treatment blood samples were interrogated using the Guardant 360 ctDNA assay for all exons of 30 known oncogenes including BRAF and for all exons with known oncogenic mutations in the COSMIC database in 40 additional oncogenes. Clinical responses were assessed at 8-week intervals by RECIST v1.1 and PFS and OS estimates were compared using log-rank test in patients with detectable versus undetectable $BRAF^{V600}$ mutant ctDNA,. **Results:** Somatic $BRAF^{V600E}$ or $BRAF^{V600K}$ ctDNA was detected in 34 of 50 patients with baseline (before lead-in cycle 1) blood samples available for analysis including 16 of 23 (70%) patients randomized to continuous dosing, 15 of 21 (71%) randomized to intermittent dosing, and 3 of 6 (50%) who were not randomized due to disease progression at 8 weeks or other factors. Four additional patients had other detectable somatic mutations but no detectable $BRAF^{V600}$ ctDNA at baseline, and 12 patients had no detectable somatic ctDNA mutations at baseline. Detection of $BRAF^{V600}$ ctDNA was associated with baseline disease stage ($p = 0.008$). There was no difference in the overall response rate based on baseline ctDNA detection. Detection of ctDNA at baseline was associated with worse PFS (median $BRAF^{V600}$ ctDNA positive = 5.8; 95% CI: 4.2-9.6 months, $BRAF^{V600}$ ctDNA negative = 21.4 mos; 95% CI 10.4-NA; measured from registration to lead-in cycle 1, $p = 0.001$) and OS ($BRAF^{V600}$ ctDNA positive = 17.8 mos; 95% CI 9.76-NA, $BRAF^{V600}$ ctDNA negative = not reached; 95% CI NA-NA, $p = 0.0021$). **Conclusions:** The absence of detectable $BRAF^{V600}$ ctDNA at baseline is associated with improved PFS and OS in patients receiving treatment with dabrafenib and trametinib. Clinical trial information: NCT02196181. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

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**10060** **Poster Session (Board #409), Fri, 8:00 AM-11:00 AM**

## Association of pathogenic germline variant KDR Q472H with angiogenesis and resistance to treatment in melanoma.

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**Background:** Preclinical data suggest that melanoma angiogenesis promotes resistance to MAPK-pathway (MAPKi) and immune checkpoint inhibitors (ICIs). However, phase II clinical trials of anti-angiogenic therapy in melanoma were disappointing. We previously identified a pathogenic germline variant Q472H in the kinase insert domain receptor [KDR Q472H; vascular endothelial growth factor receptor-2 (VEGFR-2)] in 35% of primary melanoma patients. We hypothesize that KDR Q472H promotes resistance to MAPKi or ICIs, and that combined MAPKi or ICI and VEGF pathway inhibition may improve outcomes in patients harboring the variant. **Methods:** Metastatic melanoma (MM) patient clinical data and biospecimens enrolled in the NYU Langone Medical Center Melanoma program were studied. KDR status was determined by TaqMan assays. Tumor microvessel density (MVD) was assessed by CD34 immunohistochemistry. The impact of KDR Q472H on the tumor microenvironment was determined by RNA-seq and Nanostring. Synergy between BRAF (dabrafenib) and VEGFR-2 (lenvatinib) inhibitors in KDR-genotyped MM cell lines was assessed using cell proliferation assays and the Chou-Talalay method. Synergy between ICIs and anti-VEGFR-2 was evaluated *in vivo* using a B16 melanoma model. **Results:** We studied 221 MM patients (38% KDR Q472H variants). KDR Q472H variant was significantly associated with higher tumor MVD (P = 0.002). Among the MAPKi-treated patients, KDR Q472H homozygotes had shorter median progression-free survival (PFS, 3.3 vs 9.7 months, P = 0.009) than KDR wild type (WT). In patients treated with anti-PD-1-based therapies, response rates were lower in KDR Q472H variant patients compared to WT (P = 0.012), with shorter median PFS (8.4 months vs not reached, P = 0.0443). Transcriptomic analyses identified an immunosuppressive phenotype in KDR Q472H tumors, with reduced expression of genes associated with chemotaxis, inflammation, T cell activity, and antigen presentation. Consistent with this finding, VEGFR-2 blockade in a KDR Q472H B16 mouse melanoma model augmented the anti-melanoma immune response. KDR Q472H cell lines displayed synergistic cytotoxicity with dabrafenib and lenvatinib, compared to KDR WT cells. **Conclusions:** Our data demonstrate that melanoma patients with pathogenic germline variant KDR Q472H may be more resistant to both ICIs and MAPKi. Anti-angiogenic therapy should be reconsidered within this specific subset of patients in prospective clinical trials. Research Sponsor: P50 CA225450 NYU Melanoma SPORE, P30 CA016087 Cancer Center Support Grant.

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**10061** **Poster Session (Board #410), Fri, 8:00 AM-11:00 AM**

## Integrated biomarker study of neoadjuvant pepinemab and nivolumab in patients with resectable metastatic melanoma.

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**Background:** SEMA4D has broad immunomodulatory effects in the tumor microenvironment (TME); blocking SEMA4D in combination with checkpoint inhibitors (CI) promotes immune infiltration, reduces recruitment of myeloid cells, enhances T cell activity, and promotes tumor regression. We hypothesized that adding pepinemab (VX15/2503), which targets SEMA4D, to CI would increase immunomodulatory effects and augment response in melanoma (NCT03769155). **Methods:** Patients with resectable stage IIIB/C/D melanoma were enrolled to control (no neoadjuvant therapy) or treatment cohorts (n = 8 in four cohorts of pepinemab plus nivolumab, ipilimumab, nivolumab/ipilimumab or alone). Here we report results from patients receiving two doses of nivolumab (360mg) and pepinemab (15mg/kg) every three weeks followed by surgery. Primary endpoint was T cell infiltration into the TME; secondary endpoints include pathologic response rates, peripheral immune profile, and safety. **Results:** Ten patients are reported: two were controls, eight received neoadjuvant therapy. Two patients had pathologic complete response, one had a near-complete pathologic response ( $< 1\%$ viable tumor), one had a partial response (41% viable tumor) and four had stable disease (73-90% viable tumor). All neoadjuvant patients underwent surgery without delay; one patient experienced grade 3 post-operative cellulitis. There were two treatment-related grade 3 adverse events (weakness and arthralgia). Pharmacodynamic studies confirmed saturation of PD-1 and SEMA4D in peripheral and tumor-infiltrating T cells. T/B cell ($CD8^+/CD20^+$) ratios, a surrogate for T cell infiltration, were higher in post-treatment tumors compared to pre-treatment and were higher in the tumor bed compared to normal adjacent tissue. Flow cytometric evaluation identified an increase in $CD26^{hi}$ $CD4^+$ and $CD8^+$ tumor-infiltrating effectors in treated patients compared to controls and an increase in peripheral frequencies of the PD-1-responsive effector $HLA\text{-}DR^+CD38^+Ki67^+$ $CD4^+$ and $CD8^+$ T cells following treatment. Treatment increased infiltration of myeloid populations into the TME, increased expression of PD-L1 on TME myeloid populations, and increased expression of the SEMA4D receptor Plexin-B2 on the surface of TME $CD45^-$ and M2 macrophages and MDSC. **Conclusions:** Neoadjuvant nivolumab and pepinemab results in increased T cell infiltration with excellent major response rate (38%) and expected safety profile. We continue to enroll patients using other rational combinations of pepinemab and CI. Clinical trial information: NCT03769155. Research Sponsor: Vaccinex, Inc.

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**10062** **Poster Session (Board #411), Fri, 8:00 AM-11:00 AM**

## The use of plasma proteomic markers to understand the biology of immunotherapy response.

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**Background:** Despite recent successes with immune checkpoint blockade (ICB) in melanoma, the prognosis for most patients remains dire. Whereas small fraction of patients are able to achieve disease control, most do not respond or are limited by immune-related toxicities. Robust non-invasive predictors of ICB response have the potential to guide clinical decision and alter management of patients, however, no such predictors currently exist. **Methods:** We applied a highly-multiplex Proximity Extension Assay to simultaneously detect $>$ 1000 proteins in the plasma of anti-PD-1 treated melanoma patients. Our cohort comprised 116 patients, 66 responders (R) and 50 non-responders (NR). Additional 65 patients comprised a validation cohort with 30 R and 35 NR, and included 50 patients who developed treatment-related toxicities. Plasma samples were collected at baseline, 6-weeks and 6-months after starting the treatment. A subset of patients had single-cell RNA-seq performed on tumor tissue. Group differences and treatment effects were evaluated by linear model with maximum likelihood estimation for model parameters and Benjamini and Hochberg multiple hypothesis correction. **Results:** At baseline, 6 significantly differentially expressed (DE) proteins were identified between R and NR. Elevated expression of ST2 and IL-6, two key immunoregulatory proteins were found in NR. At 6-weeks, more dynamic changes occurred and 79 significantly DE proteins were identified between R and NR, including proteins implicated in primary or acquired resistance as IL-8, MIA, TNFR1 and potential novel targets as MCP-4/CCL13, ICOSLG and VEGF. Proteomic changes identified at baseline and 6-weeks were more profound at 6-months, and moreover 238 proteins were confirmed significant between R and NR. Importantly, we were able to leverage these differences to build classifiers of R and NR subsets. We compared mRNA expression of DE proteins within the tumor microenvironment by leveraging scRNAseq data from a subset of these patients. Enriched expression of these genes was uncovered in certain myeloid and exhausted T cell subsets, thus shedding insight into the potential role of these cell subsets in ICB response. **Conclusions:** Plasma proteomic profiling of anti-PD1 treated patients identified important tumor and immune changes associated with response. Non-invasive means discovery of circulatory protein biomarkers may predict sensitivity to immunotherapy and uncover biological insights underlying primary resistance. Research Sponsor: Olink proteomics.

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**10063** **Poster Session (Board #412), Fri, 8:00 AM-11:00 AM**

## Survival analysis between narrower surgical margins and guideline-recommended margins for excision of cutaneous squamous cell carcinoma: A multicenter, retrospective study of 1,204 Japanese cases.

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**Background:** Controversy exists regarding the optimal surgical margin for cutaneous squamous cell carcinoma (cSCC). Current NCCN Guidelines recommend excision with a 4–6-mm clinical margin for low-risk cSCC and wider ( $>$ 6-mm) clinical margin for high-risk cSCC tumors. However, adherence to this guideline is often difficult, as high-risk cSCCs frequently occur on the faces of elderly patients. Thus, we aim to investigate the correlation between different surgical margins and prognosis in patients with cSCC. **Methods:** Patients with cSCC who had undergone surgical excision of the primary site between 2011 and 2019 at 11 Japanese institutions were included in this study. Patients were divided into two groups: the standard margin group (SMG) with excisions adhering to the guideline-recommended margins, and narrower margin group (NMG) with excisions with narrower margins than are guideline-recommended. Local recurrence-free survival (LRFS), relapse-free survival (RFS), and overall survival (OS) were estimated using Kaplan–Meier analysis and compared between the two groups. **Results:** A total of 1204 patients with cSCC (SMG, 637; NMG, 567) were included in this study. RFS was significantly lower in SMG than in NMG (5-year RFS 72% vs 79%; P = 0.03); however, no statistically significant differences were observed between the two groups in LRFS (5-year LRFS 80% vs 82%; P = 0.41) or OS (5-year OS 84% vs 83%; P = 0.90). Due to striking statistical significance in several characteristics of patients between the two groups, subgroup analyses, focusing on the cohort of head and neck cSCCs, were also performed. The patient characteristics were similar between SMG and NMG in both the T1-sized tumor ( $<$ 2 cm, SMG, 182; NMG, 250) and T2-sized tumor (2 cm $\leq$ tumor $<$ 4 cm, SMG, 130; NMG, 136) cohorts, based on AJCC-TNM staging (8th edition). There were also no significant differences between the SMG and NMG in LRFS (5-year LRFS, T1: 80% vs 86%; P = 0.59; T2: 85% vs 84%; P = 0.84), RFS (5-year RFS, T1: 80% vs 81%; P = 0.84; T2: 77% vs 76%; P = 0.99), or OS (5-year OS, T1: 82% vs 87%; P = 0.42; T2: 88% vs 85%; P = 0.68). Furthermore, when the NMG was divided into the two margin groups (margins reduced by $<$ 3 mm or $\geq$3 mm from the standard margin), no significant difference was observed in LRFS, RFS, and OS. **Conclusions:** This study did not reveal a significant impact of the size of clinical excision margins on survival in patients with cSCCs. Strikingly, the narrower margins may be more appropriate for $<$ 4 cm-sized head and neck cSCCs. Research Sponsor: National Cancer Center Research and Development Fund.

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**10064** **Poster Session (Board #413), Fri, 8:00 AM-11:00 AM**

## Health-related quality of life in stage III melanoma patients treated with neoadjuvant ipilimumab and nivolumab followed by index lymph node excision only, compared to therapeutic lymph node dissection: First results of the PRADO trial.

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**Background:** Neoadjuvant ipilimumab and nivolumab induces high pathologic response rates of 74-78% (OpACIN and OpACIN-neo trial), thus the role of Therapeutic Lymph Node Dissections (TLND) in patients with major pathologic responses (MPR: pathological (near) complete response) is now unclear. In the PRADO trial, TLND was omitted in patients with MPR in their index lymph node ((ILN), the largest LN marked prior to neoadjuvant therapy). We sought to determine if less extensive surgery is associated with better Health Related Quality of Life (HRQoL). These are the first results of the comparison of HRQoL between patients undergoing a TLND or less extensive ILN excision. **Methods:** HRQoL was assessed with the European Organisation for Research and Treatment of Cancer QoL questionnaire-C30 (QLQ-C30). A generalized estimation equation was used to assess the difference in HRQoL outcomes between patients who underwent TLND (pathological non- and partial-responders, pNR/pPR) versus those who did not (pathological (near)complete responders, pNCR/pCR). Differences were adjusted for age, gender and follow-up (FU, in weeks), but not for pathological responses (pNR, pPR, pNCR & pCR). Differences in QLQ-C30 scores were classified as clinically important according to published guidelines. **Results:** A total of 49 patients from the PRADO study had reached at least 24 weeks FU, and were included in the first explorative analysis. The median age of this study population was 58 years (range, 22-84). Questionnaire completion rates were high: 94% at baseline, 100%, 90%, 88% at week 6, 12 and 24, respectively. Sixteen (33%) patients underwent TLND versus 33 (67%) who had ILN excision only. Over a FU period of 24 weeks, patients who underwent TLND scored significantly lower on global (68 vs 78, adjusted difference (diff) = -9.53, p = .005), physical (84 vs 94 diff = -11.1, p = < .001), emotional (69 vs 83, diff = -11.7, p = .001), role (70 vs 85, diff = -13, p = .004), and social functioning (81 vs 91, diff = -8.9, p = .016) and had a higher symptom burden of fatigue (35 vs 23, diff = 11.1, p = .004), insomnia (38 vs 18, diff = 16.6, p = .002) and financial impact (12 vs 4, diff = 7.9, p = .027) than patients undergoing ILN excision only. These differences were indicated as clinically relevant. **Conclusions:** First results from PRADO suggest that reducing the extent of surgery following neoadjuvant immunotherapy might result in better HRQoL of high-risk stage III melanoma patients. Clinical trial information: NCT02977052. Research Sponsor: Bristol Myers Squibb.

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**10065** **Poster Session (Board #414), Fri, 8:00 AM-11:00 AM**

## Cemiplimab as first intervention for patients with locally advanced cutaneous squamous cell carcinoma.

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Cemiplimab as First Intervention for Patients with Locally Advanced Cutaneous Squamous Cell Carcinoma (cSCC) **Background:** Cutaneous squamous cell carcinoma is the second most common non-melanoma skin cancer. Early stage disease is managed with local intervention in the form of surgery or radiation and translates into cure for greater than 95% of the patients. Patients with high risk disease who have large primary lesions, neural, or nodal involvement are usually not amenable to cure with local intervention and may experience significant morbidity, disfigurement, or functional deficits. These patients had no effective systemic treatment options until recent approval of cemiplimab. We report the outcomes for upfront treatment with cemiplimab in locally advanced cSCC. **Methods:** This is a single institution retrospective study of patients with locally advanced cSCC defined as those requiring more than simple excision and/or complex repair or regional disease with nodal involvement who received at least two doses of cemiplimab between January 1, 2018 through January 17, 2020. Patients with radiologically measurable disease had response evaluated per RECIST criteria. Patients who had no measurable disease had their clinical response (complete resolution or healing of primary lesion) assessed per treating physician and need or lack of local intervention documented. Adverse events were assessed and graded per CTCAE criteria. The primary end point was to ascertain the need for local intervention. **Results:** Thirty six patients were eligible. Twenty-two (61%) patients treated with upfront cemiplimab were able to avoid local intervention with surgery and/or radiation; four patients progressed or died on treatment. Three (8%) patients received local intervention. Eleven (31%) patients are still receiving cemiplimab and local intervention decision is pending. The overall response rate was 69% and the clinical benefit rate was 92%. The median treatment duration was six months and the median number of doses received was six. Adverse events occurred in 31% of patients; the most common adverse event was dermatitis. **Conclusions:** Upfront treatment with cemiplimab in patients with locally advanced cSCC obviated need for disfiguring/complex surgery or radiation in majority of patients. Cemiplimab was tolerated well; no new safety signals were observed. Neo-adjuvant phase II study is in development. Research Sponsor: None.

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**10066** **Poster Session (Board #415), Fri, 8:00 AM-11:00 AM**

## Using digital-image analysis of tumor-infiltrating lymphocytes to predict survival outcomes in primary melanoma.

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**Background:** Inclusion of tumor-infiltrating lymphocytes (TIL) into AJCC staging criteria has been proposed due to evidence suggesting its prognostic significance. However, subjective inter-observer discordance prevents adoption of semi-quantitative TIL grading (e.g. absent, non-brisk, brisk) into clinical practice. We hypothesize that digital-image analysis (DIA) of TIL can provide a standardized, quantitative scoring system that more accurately predicts survival compared to currently used semi-quantitative grading methods. **Methods:** Clinical data and tumor specimens were analyzed from prospectively enrolled primary melanoma patients in the New York University Interdisciplinary Melanoma Cooperative Group with median follow-up of 5 years. H&E-stained slides were digitized using an Aperio ScanScope at 20X magnification. QuPath software was used for automated TIL quantification. Cox regression analysis was used to assess the improved prognostic value of TIL on recurrence-free (RFS) and overall survival (OS). Patients were separated into high- and low-TIL groups using a score threshold determined by the Youden Index. **Results:** 453 patients (18% stage I, 42% stage II, 40% stage III) were scored using automated TIL assessment and scores were significantly correlated with better RFS and OS per 10% increase in TIL (stage adjusted hazard ratio [aHR] = 0.92 [0.84-1.00] for RFS and aHR = 0.90 [0.83-0.99] for OS). A model combining TIL score with stage increased prognostic ability for both RFS (0.68 to 0.70, P = 0.02) and OS (0.62 to 0.64, P = 0.01), as assessed by concordance indices (C-index). Kaplan-Meier curves of high- ( $>$ 16.6%) versus low-TIL ($\leq$16.6%) patients showed clear separation in RFS and OS (median RFS = 155 vs 48 months, P $<$ 0.001; median OS = 155 vs 89 months, P = 0.002). For comparison, a subset of the cohort (n = 250) was semi-quantitatively graded (absent, non-brisk, brisk) by an attending melanoma pathologist; however, this did not significantly differentiate RFS between groups (P $>$ 0.05). **Conclusions:** A standardized, quantitative TIL scoring system significantly improved prediction of RFS and OS in primary melanoma patients compared with semi-quantitative TIL grading. Incorporation of quantitative TIL scoring into prognostic algorithms, such as AJCC criteria, should be considered. Research Sponsor: P50 CA225450 NYU Melanoma SPORE, Other Foundation, P30 CA016087 Cancer Center Support Grant.

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**10067** **Poster Session (Board #416), Fri, 8:00 AM-11:00 AM**

## Radiomic signatures to predict response to targeted therapy and immune checkpoint blockade in melanoma patients (pts) on neoadjuvant therapy.

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**Background:** Metastatic melanoma pt outcomes have been revolutionized by targeted therapy (TT) and immune checkpoint blockade (ICB), which are now being evaluated in the neoadjuvant (neoadj) setting. While tumor-based biomarkers may help predict response, predictors of response obtained by less invasive strategies could greatly benefit pt care and allow real-time treatment response monitoring. Radiomic signatures derived from computerized tomography (CT) images have recently been shown to predict response to ICB in stage IV pts. However, the association of radiomic features with pathological response following neoadj therapy has not been assessed. We sought to determine if radiomic assessment predicts pCR in pts receiving neoadj TT and ICB. **Methods:** We collected data for a cohort of melanoma pts with locoregional metastases who were treated with neoadj TT (n = 33) or ICB (n = 30). Pts received systemic therapy for 8-10 weeks prior to planned surgical resection. Responses were evaluated radiographically (RECIST 1.1) and via pathological assessment (evaluating for pathologic complete response; (pCR) versus < pCR). Thirty two pts (19 ICB; 13 TT) were included in the radiomics analysis based on the availability of appropriate CT imaging. A total of 310 unique radiomic features (10 histogram-based and 300 second-order texture features) were calculated from each extracted volume of interest (VOI). Feature extraction was performed on baseline and initial on-treatment pre-operative CT scans. Features associated with pCR were assessed using a feature selection approach based on Least Absolute Shrinkage and Selection Operator (LASSO). Selected features were used to build a classification model for prediction of pCR to ICB or TT. Leave-One-Out Cross-Validation was performed to evaluate the robustness of the estimates. **Results:** Out of 310 radiomic features, three features measured at baseline were able to predict a pCR to neoadj ICB or TT with sensitivity, specificity and accuracy of 100%, though these signatures were non-overlapping. In the on-treatment pre-operative scans, 3 distinct features (also non-overlapping and distinct from the predictive pre-treatment signatures) also predicted pCR to ICB and TT with 100% sensitivity, specificity and accuracy. **Conclusions:** Radiomic signatures in baseline and on-treatment CT scans accurately predict pCR in melanoma pts with locoregional metastases treated with neoadj TT or ICB. These provocative findings warrant further investigation in larger, independent cohorts. Research Sponsor: None.

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**10068** **Poster Session (Board #417), Fri, 8:00 AM-11:00 AM**

## Using a clinicopathologic and gene expression model to identify melanoma patients at high risk for disease relapse.

*Alexander M. Eggermont, Domenico Bellomo, Félicia Tjien-Fooh, Renske Wever, Enrica Quattrocchi, Sindhuja Sominidi Damodaran, Martin Van Vliet, Jvalini Dwarkasing, Alexander Meves; Princess Máxima Center, Utrecht, Netherlands; SkylineDX B.V., Rotterdam, Netherlands; Mayo Clinic, Rochester, MN*

**Background:** The identification of early stage melanoma patients at high risk for relapse is still difficult. Roughly 50% of melanoma deaths occur in patients who were initially diagnosed with nonmetastatic melanoma. Therefore, a strong clinical need has emerged for diagnostic tools that can identify melanoma patients at high risk for relapse. Here, we assessed the performance of a recently developed model (Bellomo et al., JCO Precis Oncol. 2020: in press), combining clinicopathologic and gene expression variables (CP-GEP), in identifying melanoma patients that have a high risk for disease relapse. **Methods:** We assessed the prognostic performance of the CP-GEP model in a cohort of 837 consecutive melanoma patients from Mayo Clinic who had a sentinel lymph node biopsy (SLNb) performed within 90 days of their diagnosis. The CP-GEP model combines Breslow thickness and patient age, with the expression of 8 genes in the primary tumor, to stratify patients according to their risk of relapse: CP-GEP High Risk or CP-GEP Low Risk. The main clinical endpoint of this study was five-year relapse free survival (RFS). **Results:** Patients were stratified based on SLNb status and CP-GEP classification. 76% of the patients were SLNb negative and had an RFS of 79% versus 52% for SLNb positive patients; HR, 3.21; $P < 0.0001$. 60% of the patients were identified as CP-GEP High Risk and had an RFS of 62% versus 87% for CP-GEP Low Risk patients; HR, 4.12; $P < 0.0001$. Within the SLNb negative group (637 patients of which 65% stage I), 51% of patients were classified as CP-GEP High Risk. Here, RFS was 70% for CP-GEP High Risk patients versus 89% for CP-GEP Low Risk patients; HR, 3.61; $P < 0.0001$. The prognosis of these CP-GEP High Risk patients is similar to stage IIC/IIIA patients with reported RFS ranging from 63% to 77%. This confirms the heterogeneity in prognosis among patients with stage I/II melanoma disease. **Conclusions:** The CP-GEP model can be successfully used to stratify patients based on their risk for relapse. In particular, it can be used to identify SLNb negative patients with a high risk for disease relapse who may benefit from therapeutic interventions. Independent validation studies are ongoing to validate the CP-GEP model in various patient populations. Research Sponsor: Mayo Clinic, U.S. National Institutes of Health.

| | Stratification | Number of patients | RFS | DMFS | MSS |
|---|---|---|---|---|---|
| **837 cohort** | None | 837 | 73% | 80% | 91% |
| | SLNb negative | 637 | 79% | 86% | 93% |
| | SLNb positive | 200 | 52% | 64% | 85% |
| | CP-GEP Low Risk | 337 | 87% | 92% | 96% |
| | CP-GEP High Risk | 500 | 62% | 72% | 88% |
| **637 SLNb negative** | CP-GEP Low Risk | 310 | 89% | 94% | 97% |
| | CP-GEP High Risk | 327 | 70% | 78% | 89% |

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**10069** **Poster Session (Board #418), Fri, 8:00 AM-11:00 AM**

## Vismodegib (V) for organ preservation for locally advanced (LA) orbital/periocular basal cell carcinoma (BCC).

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**Background:** LA BCC of the eye/lacrimal drainage system most often requires disfiguring radical surgery, possibly including exenteration. As an alternative to radical surgery, we evaluated ophthalmologic outcomes following treatment with V using a novel Visual Assessment Weighted Score (VAWS) in patients (pts) with locally advanced periocular BCC. **Methods:** In this open label, non-randomized trial, pts with globe- and lacrimal-threatening orbital/periocular BCC were scored with VAWS prior to treatment with 150 mg of V daily. Pts were evaluated by ophthalmic exam (OE) every 3 mo & with MRI/CT at 5-9 mo. Pts with progressive disease (PD) were offered salvage surgery. Tumor response was assessed by RECIST v1.1. Responders (CR, PR, SD) continued V if tolerating therapy. Pts with intolerable side effects stopped V & were offered surgery of their residual tumor. Post-surgical specimens were assessed for histologic presence of BCC by a dermatopathologist. The primary endpoint, maintenance of visual function, was evaluated by VAWS at final post treatment assessment (FPTA), 1 yr after the start of V or 2 mo post-surgery. A VAWS of 21/50 was considered successful, representing preservation of a functional eye. **Results:** 50 pts were planned for enrollment, but the study was stopped early for benefit. From 06/25/2015 to 05/16/2019, 35 pts signed consent; 1 was a screen failure; 34 (97%) received V & 35 were evaluable for analysis by ITT; 1 died from aspiration pneumonia. The median time on study was 261 days. Average treatment with V was 223 days. 32 (91%) underwent OE & 27 (77%) had an MRI/CT. 27 (77%) underwent surgery & 33 (94%) attained organ preservation. Overall response rate (ORR) on OE was 84% (0%-PD,6%-SD,29%-PR,54%-CR, 11% not assessed(NA)). ORR by MRI/CT was 72% (0%-PD,6%-SD, 26%-PR,46%-CR,22% NA). 31 (89%) were scored with VAWS at 3 mo & 30 (86%) at FPTA. The mean VAWS at baseline was 44/50, 46/50 at 3 mo, & 47/50 at FPTA. Of the 35 pts scored at baseline by VAWS, 1 (3%) had a major decline during follow up, 5 (14%) a minor decline, 27 (77%) stable/improved, & 2 (6%) NA. No pts experienced grade 3-5 events. Of the 27 post-surgical pathologic specimens evaluated for histological response, 67% had NED, 22% had clear margins, & 11% had BCC to the margin. Two pts have recurred & underwent Mohs surgery. **Conclusions:** Treatment with V led to organ preservation for pts with LA periocular BCC, with preservation of visual function. Vismodegib is practice changing as neoadjuvant therapy for LA BCC of the eye/lacrimal drainage system in which surgery would result in unacceptable morbidity. Clinical trial information: NCT02436408. Research Sponsor: Genetech, institutional funding from the University of Michigan.

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**10070** **Poster Session (Board #419), Fri, 8:00 AM-11:00 AM**

## Checkpoint inhibitor treatment in patients with isolated in-transit melanoma metastases.

*Lucy Storey, Mohammed Abdul-Latif, Sophia Kreft, Emma Barrett, Lisa M Pickering, Maartje W. Rohaan, Sobia Ahmed, Thomas K. Eigentler, Jessica Cecile Hassel, Sebastian Haferkamp, Frank Meiss, Theresa Steeb, Heather May Shaw, Christian U. Blank, Alexander Christopher Jonathan Van Akkooi, James M. G. Larkin, Bastian Schilling, Paul Lorigan, Paul D. Nathan; Christie NHS Foundation Trust, Manchester, United Kingdom; Mount Vernon Cancer Center, Northwood, United Kingdom; Department of Dermatology, University Hospital Würzburg, Germany, Germany; Manchester Foundation Trust, Education and Research Centre, Wythenshawe Hospital, Manchester, United Kingdom; Royal Marsden Hospital, London, United Kingdom; Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; University of Manchester, Manchester, United Kingdom; Department of Dermatology, Center for Dermatooncology, University Medical Center Tübingen, Tübingen, Germany; Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; Department of Dermatology, University Hospital Regensburg, Regensburg, Germany; Department of Dermatology and Venereology, University of Freiburg, Freiburg, Germany; Department of Dermatology, University Hospital Erlangen, Erlangen, Germany; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Netherlands Cancer Institute, Amsterdam, Netherlands; University Hospital Würtzburg, Munich, Germany; University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom; Mount Vernon Cancer Centre, Northwood, United Kingdom*

**Background:** In the context of multiple in-transit melanoma metastases without nodal involvement, a variety of treatment modalities have historically been employed including surgery, laser, isolated limb perfusion/infusion, intralesional interleukin-2, T-VEC and electrochemotherapy. Unfortunately, most patients treated with these modalities experience subsequent disease progression. While checkpoint inhibitors (CPI) are a standard of care for bulky unresectable stage III and for stage IV melanoma, patients with isolated in-transit metastases were rarely included in registration studies. There are anecdotal reports of lower response rates in these patients despite them having disease characteristics that would usually be associated with a good response. **Methods:** We report data from 11 retrospective patient cohorts treated at cancer centres across Europe who received CPI between 2016 and April 2019. All patients had multiple in-transit metastases without clinical or radiological evidence of nodal or distant disease. Disease response was assessed using CT, PET-CT or MRI depending on clinical indication. All patients had at least one prior resection of loco-regional relapsed disease and were deemed not curable by further surgery. **Results:** Sixty three patients meeting criteria were identified, 40 females and 23 males. Median age was 72 years and 54 (86%) patients had a normal lactate dehydrogenase (LDH). 19 (30%) patients had a BRAF mutation. At treatment initiation, the majority 55 (87.3%) received single agent PD-1 inhibitor, 7 (11.1%) combination ipilimumab + nivolumab and 1 (1.6%) received single agent anti-CTLA 4. The overall response rate was 62% for the full population. The response rate with anti-PD1 monotherapy was 59%. With a median FU of 23 months, the median PFS was 26 months, median OS not reached. OS estimates with 95% CI: 12 month - 93% (87-100%), 24 month - 88% (80-98%), 36 month - 80% (67-95%). **Conclusions:** The results show a high response rate to CPI in patients with in-transit metastases and support early treatment with CPI following identification of in-transit metastases not curable with surgery whilst disease characteristics remain favourable. Research Sponsor: None.

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**10072** **Poster Session (Board #421), Fri, 8:00 AM-11:00 AM**

## KRT-232, a first-in-class, murine double minute 2 inhibitor (MDM2i), for TP53 wild-type ($p53^{WT}$) Merkel cell carcinoma (MCC) after anti–PD-1/L1 immunotherapy.

*Michael K.K. Wong, Ciara Marie Kelly, Melissa Amber Burgess, Karl Lewis, Jaspreet Singh Grewal, Anthony J. Olszanski, Jesse McGreivy, Wayne Rothbaum, Hope Qamoos, James A. DeCaprio; University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY; University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA; University of Colorado Cancer Center, Denver, CO; Norton Cancer Institute, Louisville, KY; Fox Chase Cancer Center, Philadelphia, PA; Kartos Therapeutics, Inc., Redwood City, CA; Dana-Farber Cancer Institute, Boston, MA*

**Background:** MCC is an aggressive neuroendocrine skin cancer with very poor prognosis. Immune checkpoint inhibition was recently shown to benefit some patients (pts). There are few effective treatments (tx) and no standard of care for those who relapse on or are refractory to anti-PD-1/L1 agents (R/R). In $p53^{WT}$ MCC, oncoproteins from the Merkel cell polyomavirus can inhibit p53 tumor suppressor functions via L-MYC/EP400-dependent activation of MDM2. KRT-232, a potent, selective, orally available MDM2i, is being evaluated in pts with $p53^{WT}$MCC who are R/R to anti-PD-1/L1 tx. **Methods:** In stage 1 of this open-label, multicenter, phase 2 study (NCT03787602) pts initially received KRT-232 240mg QD days 1-7 of a 21 day (d) cycle (cy). This cohort was closed due to Grade (Gr) 3/4 cytopenias and pts were moved to 240mg QD days 1-5 of a 28d cy to allow for hematologic recovery. Two new arms were opened: 240mg and 180mg QD days 1-5 of a 28d cy. The primary endpoint is objective response rate (ORR) by RECIST 1.1. Secondary endpoints include duration of response, progression-free survival, overall survival, and safety and tolerability of KRT-232. **Results:** At the time of this analysis, 11 pts were treated with KRT-232: 6 on the 240mg 7/21d, 3 on the 240mg 5/28d and 2 on the 180mg 5/28d schedules. Median age was 66; 46% of pts had ECOG 1 (range 0-1), the median prior lines of systemic therapy was 3 (range 1-4) and 82% had prior radiation tx. Treatment-emergent adverse events (AEs), regardless of grade or causality, were reported in all pts: 55% had Gr 3-4 AEs and 36% had serious AEs (SAEs). The most common AEs included neutropenia (55%), anemia, leukopenia and thrombocytopenia (each 45%), diarrhea, nausea and fatigue (each 36%), and lymphopenia, hypomagnesaemia, lipase increase and sinus tachycardia (each 27%). SAEs were mainly due to cytopenias. One Gr 5 AE of respiratory failure/ascites was attributed to progression. Median time on study was 11.3 wks (range 1.3-20.9). Two of 11 pts on active tx have not yet reached the first response assessment (wk 6). Of the 9 pts who have reached wk 6, 2 PRs and 1 SD (converted to PR at wk 12) were reported. At the second response assessment (wk 12), 2 PRs were reported; one of the PRs at wk 6 has not yet reached wk 12. The ORR was 33% (3/9 pts). **Conclusions:** KRT-232 demonstrates promising monotherapy activity in MCC $p53^{WT}$ pts who failed anti-PD-1/L1 tx. This is the first clinical proof-of-concept for inhibiting the MDM2 pathway in MCC. Safety and efficacy continue to inform KRT-232 dose and schedule optimization. Clinical trial information: NCT03787602. Research Sponsor: Kartos Therapeutics, Redwood City, CA, USA.

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**10073** **Poster Session (Board #422), Fri, 8:00 AM-11:00 AM**

## Patient-reported outcomes (PROs) from the phase III IMspire150 trial of atezolizumab (A) + cobimetinib (C) + vemurafenib (V) in patients (pts) with *BRAF*$^{V600+}$ melanoma.

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**Background:** In IMspire150, A+C+V significantly improved investigator-assessed progression-free survival vs placebo (Pbo)+C+V in previously untreated pts with unresectable stage IIIc/IV *BRAF*$^{V600+}$ melanoma. PRO data from this trial are now reported. **Methods:** 514pts were randomized 1:1 to 28-day cycles of A+C+V or Pbo+C+V. Pts received C+V in cycle 1; A or Pbo was added on days 1 and 15 from cycle 2 onward. Pts completed the EORTC QLQ-C30 questionnaire on day 1 of cycle 1 (baseline), days 1 and 15 of cycle 2 and cycle 3, day 1 from cycle 4 onward, within 28-d of treatment discontinuation, and ≤6 months post-treatment. Prespecified secondary PRO endpoints were time to confirmed deterioration (TTCD; defined as time from randomization to first ≥10-point decrease from baseline held for 2 consecutive assessments, or 1 assessment followed by death on treatment) in quality of life (QoL) and physical functioning (PF). Prespecified exploratory endpoints were TTCD in role functioning (RF); mean change from baseline and percentage of pts with a clinically meaningful change (≥10 points from baseline) in QoL, PF, and RF. **Results:** Questionnaire completion rates were > 80% for most of the treatment period. At baseline, mean QoL, PF, and RF scores were moderate to high (Table). At week 6 (cycle 2), following initiation of A, QoL, PF, and RF scores declined, but returned to near-baseline levels at week 10 (cycle 3) and were largely maintained until week 36 (cycle 10), when < 50% of pts contributed data. In this time, ≥56% pts in both arms did not experience a clinically meaningful deterioration in QoL, PF, and RF. TTCD on QoL (hazard ratio [HR] 1.23; 95% CI 0.90-1.67), PF (HR 1.27; 95% CI 0.93-1.74), and RF (HR 1.15; 95% CI 0.86-1.55) favored Pbo, but only one-third of pts overall experienced a confirmed deterioration. **Conclusions:** PRO data showed that A+C+V did not worsen QoL, PF, and RF in pts with advanced *BRAF*$^{V600+}$ melanoma, thus supporting its use as a treatment option. Clinical trial information: NCT02908672. Research Sponsor: F. Hoffmann-La Roche Ltd.

| | Mean (SD) score, baseline | Mean (SD) change from baseline, week 6 | Mean (SD) change from baseline, week 10 |
|---|---|---|---|
| **A+C+V (QoL)** | 70.6 (21.4) | -9.10 (22.9) | -2.07 (20.4) |
| **Pbo+C+V (QoL)** | 70.8 (23.0) | 4.11 (21.6) | 1.43 (19.6) |
| **A+C+V (PF)** | 84.0 (20.8) | -6.55 (19.4) | 0.26 (16.7) |
| **Pbo+C+V (PF)** | 85.3 (19.0) | 1.96 (17.3) | -0.12 (15.4) |
| **A+C+V (RF)** | 79.8 (28.4) | -12.0 (30.9) | -3.63 (25.1) |
| **Pbo+C+V (RF)** | 80.1 (28.0) | 0.11 (31.0) | -0.94 (26.5) |

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**10074** **Poster Session (Board #423), Fri, 8:00 AM-11:00 AM**

## Efficacy of imiquimod in the management of lentigo maligna.

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**Background:** Lentigo maligna (LM), a melanocytic proliferation occurring on photoexposed skin, might progress to LM melanoma. Surgery is recommended as first-line treatment. However, the main challenge is the size of the excision inducing often-aesthetic injuries on the face and thus often refused by patients. The excision margins of 5 to 10 mm remain without international consensus. Several studies have shown that imiquimod induced LM regression, acting *by enhancing IFN-γ* production and effector function of T cells. The main goal of this study is to investigate the effect of imiquimod versus placebo in neoadjuvant setting to decrease the excision size as from the first surgical procedure. **Methods:** We performed a prospective, randomized, open, multicenter, phase III clinical study (NCT01720407). The health authority and ethics committee approvals were obtained and all subjects signed an informed consent. The primary endpoint was to demonstrate that in neoadjuvant situation, imiquimod could reduce the surgical excision size of LM with a healthy tissue margin of 5 mm. The main inclusion criteria were: Patients $>$ 18 years fit for surgery. LM of the head histologically confirmed and not previously treated. Surface lesion $\geq$ to 1cm² and $\leq$ to 20cm². The two treatment arms were imiquimod or placebo followed by LM excision. Imiquimod or placebo were applied once daily, 5 days/week for 4 weeks followed by 5 mm margin surgery performed four weeks after the last treatment application. For sample size, 268 patients were expected to demonstrate a difference of 15% between the two arms in a bilateral situation with an alpha risk of 5% and a beta risk of 20%. **Results:** The trial involved 273 patients, 238 (105 men (44%) and 133 women (56%), mean age of 71 $\pm$ 10.2 years, were analyzed in modified ITT. Statistical analysis was performed on 122 patients in the imiquimod arm and 116 patients in the placebo arm. For the primary endpoint, the first extralesionnal excision has been achieved for 112 (91.8%) patients in the imiquimod arm and for 98 (84.5%) placebo patients group. There was no significant difference (p value = 0.1067) between the two arms. However, regarding the surface of LM, imiquimod allowed a highly significant reduction (4.2 cm² $\pm$ 4.6 to 2.3 cm² $\pm$ 3.3) compared to LM treated by placebo (4.0 cm² $\pm$ 3.5 to 4.0 cm² $\pm$3.3; $p < 0.0001$). **Conclusions:** This randomized prospective study shows that imiquimod reduces the LM area (-50%) after one month of treatment. Reducing the surface of LM with imiquimod is not associated with a higher risk of intralesional excision (marge 5mm), with a significant esthetic result (less excised surface). Clinical trial information: NCT01720407. Research Sponsor: French Hospital Clinical Research Program in Cancer.

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**10075** **Poster Session (Board #424), Fri, 8:00 AM-11:00 AM**

## Adjuvant crizotinib in high-risk uveal melanoma following definitive therapy.

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**Background:** Uveal melanomas (UM) measuring at least 12mm in base diameter with a class 2 signature as defined by gene expression profiling (DecisionDx-UM) are characterized by high metastatic risk, with a median time to recurrence of 32 months. No therapy has been shown to reduce this risk. The growth factor receptor Met is highly expressed in UM. We have previously shown that crizotinib, an inhibitor of Met, is an effective adjuvant therapy in preclinical models *(Surriga et al, Mol Cancer Ther 2013).* We therefore conducted a phase II study of adjuvant crizotinib in high-risk UM. **Methods:** Eligibility included: primary lesion $\geq$12mm in base diameter; class 2 by DecisionDx-UM testing; definitive therapy within 120 days before starting crizotinib; and, no evidence of metastatic disease. Patients (pts) received 12 four-week cycles of crizotinib (250 mg twice daily). Surveillance imaging (chest CT and MRI abdomen/pelvis) were performed q3 months. The primary endpoint was distant relapse-free survival (RFS). Secondary endpoints were overall survival (OS) and toxicity. We hypothesized that the addition of crizotinib would increase the 32 month RFS from 50% to 75% ($\alpha = 0.05$; $\beta = 0.11$). **Results:** As of 1/31/2020, 34 pts had enrolled and received at least one dose of study drug with median age of 60 (range, 26-86); 41% female; and median ECOG PS 0 (range, 0-1). 2 pts could not be evaluated for the primary endpoint due to early withdrawal and loss to follow-up. The median time from primary treatment to crizotinib initiation was 60 days (range, 0-106). All pts experienced a treatment-related adverse event (AE) of any grade. 11/34 (32%) experienced a grade 3 or 4 AE, the most common being transaminase elevation (n = 8/11). 9 pts (28%) did not complete the full 48-week treatment course due to disease recurrence (n = 5) or toxicity (n = 4). An additional 5 pts required dose reduction due to hepatic toxicity or diarrhea. 15/32 evaluable pts developed distant disease relapse, with 14 developing relapse within 32 months. With a median duration of follow up of 28.7 months, the median RFS was 30.6 months (95% CI: 27.8-58.5%). The median OS was not reached. **Conclusions:** The use of adjuvant crizotinib in patients with high-risk UM did not reduce rates of relapse in this multicenter, single arm trial. 9/32 (28%) pts required dose modification or discontinuation due to AE which may have limited efficacy. Further investigations of adjuvant treatment options are warranted. Clinical trial information: NCT02223819. Research Sponsor: Pfizer Inc., Columbia University

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10076 Poster Session (Board #425), Fri, 8:00 AM-11:00 AM

# Effect of automated TIL quantification in early-stage melanoma on accuracy of standard T staging using AJCC guidelines.

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**Background:** Patients diagnosed with early stage melanoma are at risk of recurrence and death. Adjuvant therapy decreases risk but incurs toxicity and expense. While tumor-infiltrating lymphocytes (TILs) improve prognosis, studies have shown conflicting results due, at least in part, to inter-observer variability. Thus, TILs are not included in standard American Joint Committee on Cancer (AJCC) staging. Here, we quantitatively analyze TILs in hematoxylin and eosin (H&E) melanoma images using two machine learning algorithms. **Methods:** H&E images were evaluated by two methods for patients with resectable stage I-III melanoma from Columbia (N = 81) and validated using samples from Geisinger and Moffitt (N = 128). For both methods, H&E images were manually annotated using open source software, QuPath, to specify tumor regions. For Method A, images were divided into patches and, for each patch, a probability was generated to detect lymphocytes. Patches above a set threshold were considered to be "TIL positive". Ratio of TIL positive patches to total patches was assessed for every image. For Method B, a classifier was manually trained in QuPath and then applied on each image to determine the ratio of the areas of all immune cells to all tumor cells as previously published. Cutoff values to define high and low risk groups were established based on a test set and then validated in an independent cohort. **Results:** Both methods distinguished patients with visceral recurrence from those without for the Columbia training set (Method A p = .0015, Method B p = .043). Using Method A, Kaplan-Meier curve at the selected cutoff also correlated significantly with disease specific survival (DSS) for Columbia (p = .022) and was validated in the Geisinger/Moffitt (p = .046) cohort. Cox analysis using Method A showed that TIL status predicted DSS in the validation set (p = .047) and added significantly to depth and ulceration (HR = 3.43, CI: 1.047-11.257, p = .042). **Conclusions:** Both open source machine learning algorithms find significantly higher TILs in patients who do not develop metastasis. Notably, Method A may add to standard predictors, such as depth and ulceration. These results demonstrate the promise of computational algorithms to enhance visual grading, and suggest that digital TIL evaluation may add to current AJCC staging. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Melanoma Research Alliance.

**Multivariable Cox table for validation cohort using Method A.**

| | Hazard Ratio | 95% CI | *P* |
|---|---|---|---|
| **TIL Score** | 3.43 | 1.047 to 11.257 | 0.042 |
| **Depth** | 1.09 | 1.010 to 1.183 | 0.028 |
| **Ulceration** | 2.66 | 1.420 to 4.973 | 0.002 |

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**10077** **Poster Session (Board #426), Fri, 8:00 AM-11:00 AM**

## Incidence and trends of skin cancer in the United States, 1999-2016.

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**Background:** Cutaneous skin cancer is among the most common malignancies in US. While Surveillance, Epidemiology and End Results (SEER) data are vital to estimate its incidence, delays and underreporting remained major limitations. Surveillance is hindered due to exclusion from states' reportable diseases and possible outpatient diagnoses' omission from registries. Thus, exact incidence has not been known. This study determined skin cancer incidence and trends from 1999 to 2016 in a nationally representative sample. **Methods:** New melanoma, non-melanoma and other skin cancer cases among adults aged ≥20 years were identified in the National Health and Nutrition Examination Survey (NHANES), 1999-2016. Crude and age-adjusted incidences and 95% CIs were estimated by survey year cohorts (1999-2008 and 2009-2016) based on the 2000 US standard population. Sex and age-stratified longitudinal trends were examined in age and sex-adjusted regression models. Statistical analyses accounted for complex survey design with examination sample weight and adjusted for nonresponse. Sensitivity analyses included unadjusted, sex- and age- adjusted modeling. Statistical significance was determined by 2-sided *p*-value of .05. **Results:** Among 47,172 adults and 21,192 non-Hispanic whites from 1999-2016, the overall age-standardized incidences of skin cancer per 100000 persons were 390.9 (95% CI: 312-469.7) and 519 (95% CI: 413.8-624.3), respectively. The median age at first diagnosis was 72.2 (mean = 69.8, IQR = 57.5-79.5 years). The incidence was higher in men than women (474.7 vs 313.8 per 100000 persons, $p < .001$) and increased with older age ($p < .001$). Between 1999-2008 and 2009-2016, the incidence was significantly higher in those older than 70, 75 and 80 ($p \leq .01$). Rising incidence was also observed in overall population, women, and by approximately 90% among those older than 70. Sensitivity analyses showed similar trends. **Conclusions:** Our incidence rates for skin cancer were high, particularly in the elderly. From 1999 to 2016, the incidence increased in women and those 70 and older, a concerning observation given the aging population. As understanding susceptible groups has public health implications, our study provided an updated depiction of skin cancer incidence and trends in US. Research Sponsor: None.

**Trends in incidence of skin cancer per 100000 persons among US adults 20 Years and older by sex and age group, 1999-2016.**

| | 1999-2008 | 2009-2016 | p for trend |
|---|---|---|---|
| **Overall** | 299.4 | 491.1 | 0.02 |
| **Men** | 382.9 | 574.7 | 0.12 |
| **Women** | 222.9 | 414.0 | 0.03 |
| **≥ 70 y** | 1278.1 | 2424.9 | < 0.01 |
| **≥ 75 y** | 1481.2 | 3592.6 | < 0.01 |
| **≥ 80 y** | 2200.3 | 5403.2 | < 0.01 |

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**10078** **Poster Session (Board #427), Fri, 8:00 AM-11:00 AM**

## Exploring the clinical efficacy of the total body skin exam.

*Tanner Harding, Jennifer Seyffert, Brittany Maner, Anuj Kunadia, Shawn Camner, Martin Yungmann, Murray Cotter, James A. Solomon; University of Central Florida College of Medicine, Orlando, FL; Kansas City University of Medicine and Biosciences- Advanced Dermatology and Cosmetic Surgery, Department of Dermatology, Orlando, FL; Ross University School of Medicine, Miramar, FL; Advanced Dermatology and Cosmetic Surgery, Maitland, FL; Ameriderm Research, Ormond Beach, FL*

**Background:** The clinical efficacy of the total body skin exam has long been the subject of debate. A 2016 report by the United States Preventative Services Task Force (USPSTF) found the current body of evidence was "insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in [asymptomatic] adults." However, the USPSTF based its recommendations on studies evaluating mainly the ability of primary care physicians to diagnose melanoma through total body skin exams (TBSE). This study seeks to address this insufficiency in the current literature by exploring the clinical efficacy of the dermatology provider performed TBSEs as a screening tool with respect to the detection of malignant melanoma (MM), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). **Methods:** A search was performed within the electronic medical record of a large multi-state dermatology group practice for all instances of new and established patient office visits occurring from 1 January 2018 to 31 December 2019. Per practice policy, it is denoted whether each office visit includes a TBSE or partial skin exam (PSE). The number of MM, SCC, and BCC diagnoses made within the context of each class of skin exam was analyzed. **Results:** Of the 930,706 office visits analyzed, 438,027 TBSEs and 492,679 PSEs were performed. For each of the three types of skin cancer surveyed, the number of cancers diagnosed in the context of a TBSE was significantly greater than the number diagnosed in the context of a PSE. One MM was diagnosed per 161.0 TBSEs and 371.3 PSEs ($X^2$ ($df = 1$, $N = 930706$) = 662, $p < 0.001$). One SCC was diagnosed per 56.7 TBSEs and 108.4 PSEs ($X^2$ ($df = 1$, $N = 930706$) = 1258.5, $p < 0.001$). One BCC was diagnosed per 10.2 TBSEs and 17.8 PSEs ($X^2$ ($df = 1$, $N = 930706$) = 5884, $p < 0.001$). **Conclusions:** Skin cancer is detected at significantly higher rates in TBSEs than PSEs. The finding that one MM is detected in 161 TBSEs may be compared to one cervical cancer is detected in 3,776 Pap smears. Thus, a TBSE is 23.5 times more likely to identify a MM than a Pap smear is to identify a cervical cancer. This trend holds even when adjusted for prevalence. Further analysis will allow for the comparison of exam types with respect to patient age, staging, lesion size, and Breslow depth at time of cancer diagnosis. This continued analysis will allow for a more detailed risk benefit-analysis and insight into the clinical efficacy of the TBSE. Research Sponsor: None.

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**TPS10079** **Poster Session (Board #428), Fri, 8:00 AM-11:00 AM**

## Design and rationale of MASTERKEY-115 phase II trial of talimogene laherparepvec (T-VEC) with pembrolizumab (pembro) in patients with advanced melanoma who progressed on prior anti-programmed cell death-1 (anti-PD-1) therapy.

*Jason Alan Chesney, Mohammed M. Milhem, Marya F. Chaney, Priya Gokani, Wendy Snyder, Caroline Robert; James Graham Brown Cancer Center, University of Louisville, Louisville, KY; Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; Merck & Co., Inc., Kenilworth, NJ; Amgen, Inc., Cambridge, United Kingdom; Amgen, Inc., Thousand Oaks, CA; Gustave Roussy and Paris-Saclay University, Villejuif, France*

**Background:** Treatment options are limited for patients with advanced metastatic or unresectable melanoma, especially after anti-PD-1 failure. T-VEC is an intralesional oncolytic viral immunotherapy designed to selectively replicate in tumor cells and induce local and systemic antitumor response. Pembro promotes T cell activity by blocking PD-1 receptors. Combining T-VEC and pembro may produce robust antitumor activity by increasing T cell activation and blocking T cell inhibition, with a tolerable safety profile. The MASTERKEY-115 trial will evaluate safety and efficacy of T-VEC combined with pembro in patients with advanced melanoma who experienced progressive disease (PD) on prior anti-PD-1 therapy. **Methods:** NCT04068181 is a phase 2, open-label, single-arm, multicenter trial of T-VEC with pembro in patients with advanced melanoma and PD on prior anti-PD-1. The study is expected to enroll approximately 100 patients and comprises 4 cohorts. Cohorts 1 and 2 will receive anti-PD-1 in a locally recurrent or metastatic setting and experienced PD within 12 weeks of the last anti-PD-1 dose (Cohort 1: PD or stable disease prior to confirmed PD; Cohort 2: complete or partial response prior to confirmed PD). Cohorts 3 and 4 will receive adjuvant anti-PD-1 and were disease-free for $<$ 6 months (Cohort 3) or $\geq$ 6 months (Cohort 4) prior to confirmed PD. Enrollment criteria include adults with histologically confirmed unresectable or metastatic stage IIIB–IVM1d melanoma, measurable and injectable disease, ECOG PS 0-1, and prior anti-PD-1 ($\geq$ 2-3 consecutive cycles within 8 weeks, immediate prior treatment before enrollment). The primary endpoint is objective response rate per modified RECIST. Key secondary endpoints assess efficacy (objective response rate, best overall response, complete response rate, response duration, durable response rate, disease control rate, progression-free survival, overall survival), safety (incidence of treatment-emergent and treatment-related adverse events, abnormal laboratory tests), and time to subsequent anticancer therapy. The study began enrolling patients in January 2020 and enrollment is ongoing. Clinical trial information: NCT04068181. Research Sponsor: Amgen, Inc.

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**TPS10080** **Poster Session (Board #429), Fri, 8:00 AM-11:00 AM**

## A phase I study of CX-4945 administered orally twice daily to patients with advanced basal cell carcinoma.

*Zeynep Eroglu, Charles Lance Cowey, John Soong, Daniel McCormick, Phoebe Fan, Jimmy Chen, Mohamed Elgendy, Sekwon Jang, Anne Lynn S. Chang; Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Baylor-Sammons Cancer Ctr TOPA, Frisco, TX; Senhwa Biosciences, San Diego, CA; Senhwa Biosciences, New Taipei City, Taiwan; Inova Schar Cancer Institute, Fairfax, VA; Department of Dermatology, Stanford University School of Medicine, Redwood City, CA*

**Background:** Smoothened inhibitors (SMOi) targeting the Hedgehog (Hh) pathway have been approved for the treatment of patients with locally advanced Basal Cell Carcinoma (laBCC) or metastatic BCC (mBCC). Unfortunately, resistance against SMO inhibitors (SMOi) can develop. Targeting the signaling cascade downstream of SMO, in this case via a novel small molecule inhibitor, could obviate this issue. Casein Kinase 2 (CK2) affects the terminal component of the Hh signaling pathway by promoting Gli2 stability and Gli2's interaction with target genes. Given the interplay between CK2 and GLI-2 and the importance of Hh signaling activation, CX-4945, a potent CK2 inhibitor, may provide benefits for the BCC patients with resistance or intolerance to SMOi. **Methods:** A phase I trial (NCT03897036) to explore various treatment durations of CX-4945 was designed for patients with laBCC or mBCC; with endpoints include safety (CTCAE v5) and objective response rate by RECIST 1.0 for mBCC and composite response for laBCC. Major eligibility criteria include progression or intolerability to SMO inhibitors; laBCC patients must not be surgical candidates and must have received prior radiation unless contraindicated, and basosquamous histology is excluded. The first phase of the trial uses a 3+3 design to test the tolerance of a CX-4945 dose of 1000 mg bid for a duration of 28 days continuously. If 2 out of 3, or 2 out of 6 patients experience a DLT, the regimen of 1000 mg bid for 21 days followed by 7 days off (already tested in prior CX-4945 Phase I trials in other tumor types) will be selected as the recommend phase 2 dose (RP2D). Upon determining the RP2D, a dose-expansion phase will further evaluateCX-4945 in two cohorts (laBCC & mBCC), with 10 patients enrolled in each. Currently, we are enrolling patients and collecting sufficient data for the determination of RP2D in this patient population; thus, further assessments are required to determine the safety, tolerability, and efficacy of CX-4945 in advanced BCC. Clinical trial information: NCT03897036. Research Sponsor: Senhwa Biosciences.

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**TPS10081** **Poster Session (Board #430), Fri, 8:00 AM-11:00 AM**

## A phase II study evaluating atezolizumab (A), cobimetinib (C), and vemurafenib (V) in patients (pts) with BRAF-mutant melanoma and central nervous system (CNS) metastases (mets).

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**Background:** CNS mets, a common complication of melanoma, are associated with poor survival prognosis (median of 4-5 months). The rationale for combining PD-L1 pathway blockade using atezolizumab (A) with the small molecule *BRAF* pathway–targeted inhibitors cobimetinib (C) and vemurafenib (V) for the treatment of $BRAF^{V600}$ mutation–positive melanoma is based on preclinical and translational evidence supporting the synergistic antitumoral effects of these approaches. Recently, the phase 3 IMspire150 study (NCT02908672) demonstrated improved progression-free survival outcomes with A + C + V vs C + V. **Methods:** This phase 2 study (NCT03625141) is currently evaluating A + C + V in pts with $BRAF^{V600}$ mutation–positive advanced melanoma and CNS mets. The study originally included a parallel cohort evaluating A + C in pts with $BRAF^{V600}$wild-type advanced melanoma and CNS mets. This cohort was closed at an enrollment of 15 pts after the primary analysis of the phase 3 IMspire170 study (NCT03273153), which showed no added benefit with A + C vs pembrolizumab in pts with $BRAF^{V600}$ wild-type disease. Eligible pts are aged $\geq$18 years with histologically confirmed melanoma and magnetic resonance imaging–confirmed brain mets $\geq$5 mm in at least 1 dimension. In addition, pts should not have received prior systemic treatment for metastatic disease; they were required to have ECOG performance status $\leq$2 and adequate hematologic and end organ function. Prior stereotactic or surgical therapy of $\leq$10 brain mets is allowed. The primary endpoint is intracranial objective response rate (ORR) with A + C + V in $BRAF^{V600}$mutation–positive melanoma as assessed by an independent review committee. Key secondary endpoints include investigator-assessed intracranial ORR, extracranial ORR, overall ORR, safety, and quality of life. Exploratory biomarker analyses are planned. The sample size for the cohort will be approximately 60 pts. No formal statistical hypothesis is being tested in this study. The primary study analysis and the analyses of all efficacy endpoints and safety summaries will be based on data collected $\leq$6 months after the last pt is enrolled. Clinical trial information: NCT03625141. Research Sponsor: F. Hoffmann-La Roche Ltd.

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**TPS10082** **Poster Session (Board #431), Fri, 8:00 AM-11:00 AM**

## A phase II trial of nivolumab in combination with talazoparib in unresectable or metastatic melanoma patients with mutations in BRCA or BRCAness.

*Tamara A. Sussman, Wei Wei, Brian Hobbs, C. Marcela Diaz-Montero, Ying Ni, Joshua Arbesman, Jennifer S. Ko, Brian Gastman, Pauline Funchain; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Cleveland Clinic Lerner Research Institute, Cleveland, OH; Genomic Medicine Institute, Cleveland Clinic Lerner Research Institute, Cleveland, OH; Cleveland Clinic, Cleveland, OH*

**Background:** Melanoma has a response rate of 10-15% with anti-PD-1 re-challenge in the refractory setting. Newer targeted therapies in melanoma are needed, especially once patients progress on immune checkpoint inhibitor (ICI) therapy. Analysis of TCGA and the Cleveland Clinic's Gross Family Melanoma Registry reveals that a significant proportion (~40%) of melanoma patients possess somatic (31.6%) or germline (TCGA: 4.2%; Registry: 8.3%) mutations in homologous recombination repair genes, which may serve as a therapeutic target. PARP inhibitors, specifically talazoparib, have demonstrated synthetic lethality, potent PARP trapping activity, and increased immunogenicity of tumor cells by promoting T cell and NK cell infiltration *in vitro* and *in vivo*. Moreover, augmentation of the STING pathway via PARP inhibition modulates the tumor microenvironment, impacting PD-L1 expression and type I interferon production. Therefore, the use of talazoparib in combination with the ICI, nivolumab, may have a synergistic immunomodulatory and antitumor effect. **Methods:** This phase II, single arm, open label trial aims to enroll 37 primary or recurrent unresectable or metastatic melanoma patients harboring a somatic or germline mutation or deletion in *BRCA* or *BRCA*ness (genes including *ARID1A/B/2, ATM, ATR, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CDK4/12, CHEK1/2, DSS1, EMSY, ERCC3, FANCA/D2, HDAC2, IDH1, LIG3/4, MDC1, MLH1/3, MRE11, NBN, PALB2, PRKDC, RAD50/51/54, XRCC6*) who have progressed on prior ICI therapy. Patients will be treated with nivolumab 480mg IV every 4 weeks and talazoparib 1mg PO daily. The primary objective is to determine clinical efficacy of the combination therapy, as measured by the objective response rate. The trial is designed to test the null hypothesis that ORR $\leq$ 10% and is powered to detect an effect size of ORR $\geq$ 30%. Secondary objectives include PFS, OS, immune-related objective response rate (irORR), irPFS, and treatment-related adverse events. Associations with clinical response will be assessed with correlative studies of PD-L1 expression, ctDNA, tumor mutational burden, copy number variation, and the phenotypic and functional characterization of circulating and tumor infiltrating immune cells. The study is currently open and enrolling patients. Clinical trial information: NCT04187833. Research Sponsor: Pfizer, Internal funding.

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**TPS10084** **Poster Session (Board #433), Fri, 8:00 AM-11:00 AM**

## A phase III, randomized, double-blind study of adjuvant cemiplimab versus placebo post-surgery and radiation therapy (RT) in patients (pts) with high-risk cutaneous squamous cell carcinoma (CSCC).

*Danny Rischin, Matthew G. Fury, Israel Lowy, Elizabeth Stankevich, Hyunsil Han, Sandro Porceddu; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ; School of Medicine, University of Queensland, Herston, Queensland, Australia, Department of Radiation Oncology, Princess Alexandra Hospital, Woolloongabba, Australia*

**Background:** CSCC is the second most common skin cancer. While the surgical cure rate for CSCC is $>$ 95%, a proportion of pts are considered to have high risk for recurrence as assessed by immune status, primary disease stage, extent of nodal involvement, presence of extracapsular extension, and prior treatment. Post-operative RT is recommended for pts with high-risk features, but relapse with locoregional recurrence or distant metastases may still occur. This study evaluates the efficacy of cemiplimab, a human anti–PD-1 monoclonal antibody, as an adjuvant therapy for pts with CSCC with high-risk features, after surgery and RT. **Methods:** This randomized, placebo-controlled, double-blind, multicenter, Phase 3 study will evaluate cemiplimab as an adjuvant treatment for pts with high-risk CSCC, based on surgical and clinicopathologic findings, who have completed surgery and post-operative RT (NCT03969004). Immunocompromised pts were excluded. The trial will enrol 412 pts from about 100 sites in North America, Europe, and Asia-Pacific regions. Pts with at least one of the following high-risk features are eligible: a) nodal disease with extracapsular extension b) in-transit metastases c) T4 lesion d) perineural invasion, and e) recurrent CSCC with at least one other risk factor. In Part 1 (blinded), pts will be randomized 1:1 to receive cemiplimab 350 mg or placebo intravenously every 3 weeks (Q3W) for up to 48 weeks. In optional Part 2 (unblinded), pts in the placebo arm who experience disease recurrence or pts in the cemiplimab arm who experience disease recurrence $\geq$3 months after completion of 48-week treatment in Part 1 will be eligible to receive open-label cemiplimab 350 mg Q3W for up to 96 weeks. Key objectives are to compare disease-free survival (primary) as well as overall survival, freedom from locoregional relapse, and distant relapse (secondary) of adjuvant cemiplimab vs placebo in pts with high-risk CSCC. This study is currently open for enrollment. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceutical, Inc. and Sanofi.

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**TPS10085** **Poster Session (Board #434), Fri, 8:00 AM-11:00 AM**

## A phase II study of anti-PD1 monoclonal antibody (Nivolumab) administered in combination with anti-LAG3 monoclonal antibody (Relatlimab) in patients with metastatic melanoma naive to prior immunotherapy in the metastatic setting.

*Anjali Rohatgi, Ryan Campbell Massa, William E. Gooding, Tullia C. Bruno, Dario Vignali, John M. Kirkwood; UPMC Hillman Cancer Center, Pittsburgh, PA; University of Pennsylvania, Philadelphia, PA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; University of Pittsburgh, Pittsburgh, PA; Melanoma Program, UPMC Hillman Cancer Center, Pittsburgh, PA*

**Background:** Novel checkpoint inhibitors are a promising treatment for advanced melanoma, as only a fraction of patients have durable responses to current FDA-approved immunotherapy. Lymphocyte activation gene 3 (LAG3) is an inhibitory checkpoint receptor on CD4+ and CD8+ T cells, where engagement results in suppression of T cell activation and proliferation. LAG3 and PD1 are co-expressed on T cells during T cell receptor signaling and are down-regulated after antigen clearance. Persistent stimulation leads to prolonged LAG3 and PD1 expression and to T cell exhaustion, a possible mechanism of resistance to immunotherapy. Both LAG3 and PD1 are expressed on tumor-infiltrating T cells in melanoma. Murine tumors treated with both anti-LAG3 and anti-PD1 have demonstrated increased tumor regression than tumors in mice treated with either single agent. Further, a phase I trial has demonstrated safety of combined anti-LAG3 monoclonal antibody, relatlimab and anti-PD1 monoclonal antibody, nivolumab. **Methods:** This phase II, single-center clinical trial is designed to enroll treatment naive patients with unresectable or metastatic melanoma to ultimately receive combined relatlimab and nivolumab after a lead-in arm where patients are randomized to receive relatlimab, nivolumab, or the combination for the first 4 week cycle. For the lead-in phase, patients will have baseline and post-treatment blood and tumor sampling. Disease assessment by imaging will occur after the lead-in phase at 4 weeks. After completion of the lead-in phase, all patients proceed to combination therapy with disease assessment at 12-week intervals. The primary endpoint for the lead-in phase is to evaluate changes in immune cell populations in peripheral blood and tumor with the single agents and combination treatment. The primary endpoint for the combination phase is best overall anti-tumor response. Secondary clinical endpoints include progression-free survival, overall survival, duration of response and toxicity. Exploratory endpoints are to determine the mechanistic effects of anti-LAG3 and anti-PD1 on the blood and tumor microenvironment, cytokine signatures, and correlation of these with clinical response. The study is currently accruing with enrollment of 9 out of 42 patients. Clinical trial information: NCT03743766. Research Sponsor: Bristol-Meyers-Squib.

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**TPS10086** **Poster Session (Board #435), Fri, 8:00 AM-11:00 AM**

## A phase Ib study of endogenous SLC45A2-specific cytotoxic T cells for the treatment of patients with metastatic uveal melanoma.

*Suzanne Phillips, Gregory Lizee, Courtney Brown, Jacqueline Marie Lara, Roland L. Bassett, Lisa G Beal, Ravi Murthy, Amjad Talukder, David H Hawke, Ivy Lai, Patrick Hwu, Cassian Yee, Sapna Pradyuman Patel; MD Anderson Cancer Center, Houston, TX; Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Overall survival (OS) for patients (pts) with advanced uveal melanoma (UM) is poor with a median survival of approximately 12 months. Roughly half of all pts with UM will develop distant metastatic disease despite effective treatment of the primary site. Metastatic UM has a 90% prevalence of liver involvement. Currently, there are no specific FDA-approved treatments for metastatic UM and consensus guidelines recommend participation in a clinical trial. Modern treatments such as check-point inhibitors and targeted therapy have less impressive outcomes in UM. Our group has identified peptide epitopes of SLC45A2, a melanosomal transport protein, that is highly expressed in UM and present at very low levels in normal melanocytes. We demonstrated that cytotoxic T cells against SLC45A2 were able to kill HLA-matched UM cell lines. Through the use of enabling technologies, SLC45A2-specific cytotoxic T cells can be isolated and expanded ex-vivo from peripheral blood for use in endogenous T cell (ETC) therapy (a form of adoptive cellular therapy). These activated ETCs can then be infused to traffic to tumor sites. CTLA4 is a T-cell surface protein that binds to B7 with a higher affinity than the costimulatory receptor CD28, providing an inhibitory signal to T-cells. Anti-CTLA4 blockade can divert this inhibition and release the brake on antigen-specific T-cell activation of ETC. We hypothesize that antigen-specific ETCs infused via hepatic artery will be safe and tolerable for UM pts with liver metastasis. **Methods:** We are conducting a first-in-human clinical trial (NCT03068624 ) of ETC therapy targeting SLC45A2 in combination with anti-CTLA4 in pts with metastatic UM. Pts who express HLA-A*02:01 or A*24:02 undergo apheresis to collect T cells. Their cells then undergo ex vivo cloning and interleukin-21 primed expansion. Hepatic arterial infusion of ETCs will ensure direct localization to the target organ of interest. Conditioning with low-dose cyclophosphamide (300 mg/m2) occurs on Day -2. Hepatic arterial infusion of ETCs on Day 0 is followed by low dose subcutaneous interleukin-2 (IL-2) twice daily for 14 days. The initial dose escalation phase is a 3+3 design with a starting dose level of $3.3 \times 10^9$ cells/$m^2$ of ETCs alone. Once the maximum tolerated dose of ETCs is established, the dose expansion phase will include ETCs in combination with anti-CTLA4 (Ipilimumab). The primary objective is to evaluate the safety of this first in human T cell regimen. Secondary objectives are to evaluate the in vivo persistence and anti-tumor efficacy. Clinical trial information: NCT03068624. Research Sponsor: U.S. National Institutes of Health, Other Government Agency, NCI MD Anderson SPORE in Melanoma.

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**TPS10087** **Poster Session (Board #436), Fri, 8:00 AM-11:00 AM**

## Personalized combination of neoadjuvant domatinostat, nivolumab and ipilimumab in macroscopic stage III melanoma patients stratified according to the interferon-gamma signature: The DONIMI study.

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**Background:** Previous OpACIN and OpACIN-neo studies, investigating neoadjuvant ipilimumab (IPI) plus nivolumab (NIVO), demonstrated high pathologic response rates (74-78%) and favorable long-term outcomes in patients (pts) achieving pathologic response; at 36 and 18 months follow-up, respectively, only 1/71 (1.4%) pts with response has relapsed. In contrast, pts without pathologic response (pNR) have a poor prognosis; 15/23 (65.2%) have relapsed so far. This emphasizes the need for baseline biomarkers predictive of non-response and new neoadjuvant treatment combinations for these pts. In our previous studies, baseline interferon-gamma (IFN-γ) signature low pts were less likely to respond to neoadjuvant IPI plus NIVO. The DONIMI study tests the combination of NIVO +/- IPI with domatinostat (DOM), a class 1 histone deacetylase inhibitor, according to the IFN-γ signature in the tumor. Based on the signature previously described by Ayers et al. we have developed a neoadjuvant IFN-γ signature algorithm that will be used for the first time to classify pts in this prospective trial.
**Methods:** The aim of this two-center investigator-initiated phase 1b study is to assess the safety and feasibility of neoadjuvant NIVO +/- DOM +/- IPI in 45 stage III melanoma pts with RECIST 1.1 measurable de-novo or recurrent disease. IFN-γ signature high pts (n = 20) will be randomized (stratified by center) to Arm A (2 cycles NIVO 240mg q3wk) or Arm B (2 cycles NIVO 240mg q3wk + DOM 200mg twice daily (BID), d1-14, q3wk). IFN-γ signature low pts (n = 25) will be randomized to Arm C (2 cycles NIVO 240mg q3wk + DOM 200mg BID, d1-14, q3wk) or Arm D (2 cycles NIVO 240mg q3wk + IPI 80mg q3wk + DOM 200mg once daily (OD), d1-14, q3wk). Based on safety data of the first 5 pts in arm D, the remaining pts will be treated with either a higher dosing scheme (200mg BID, d1-14, q3wks), a lower dosing scheme (100mg OD, d1-14, q3wks) or the same dosing scheme (200mg OD, d1-14, q3wks). The primary endpoint is safety and feasibility. A treatment arm will be declared as not feasible if 2/5 or 3/10 pts cannot adhere to the preplanned time of surgery (week 6 +/- 1week) due to treatment-related adverse events. Biopsies (week 0, 3), blood samples (week 0, 3, 6, 12) and feces (week 0, 3, 6) will be collected for translational research. The first patient was enrolled on January 23$^{th}$, 2020. Clinical trial information: NCT04133948. Research Sponsor: 4SC.

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**TPS10088** **Poster Session (Board #437), Fri, 8:00 AM-11:00 AM**

## A phase II study of neoadjuvant pembrolizumab and lenvatinib for resectable stage III melanoma: The neopele study.

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**Background:** Recent clinical trials of neoadjuvant (neo-adj) ipilimumab combined with nivolumab (OpACIN & OpACIN-neo) in resectable stage III melanoma show that a pathological response ( $<$ 50% viable tumour at the tumour bed as determined by histopathological analysis) is associated with a prolonged relapse-free survival compared to no pathological response. Furthermore, recurrences seldom occur in those who have a pathological response following neo-adj immunotherapy with only 1/71 pts (1.4%) having recurred. In contrast, 15/23 (65.2%) pts with no pathological response have relapsed to date. The NeoPeLe trial will test the hypothesis that the synergistic combination of PD-1 blockade (pembrolizumab) with anti-angiogenic/multiple RTK inhibitor (lenvatinib) will result in a high rate of pathological response in the resected surgical specimen with a low rate of toxicity. Tissue and blood biomarkers are drawn at several timepoints and correlated to clinical and pathological endpoints to explore mechanisms of response and resistance. We will compare pathological response rate, and other clinical outcomes in this study, with previously published neo-adj clinical trials to select the best schedules for larger-scale clinical testing. Across neo-adj studies, we will also analyse the tissue collected to explore determinants of the optimal therapy for individual pts, whilst minimising toxicity.
**Methods:** Eligible pts with stage IIIB/C/D, resectable and measurable (RECIST 1.1) nodal metastatic melanoma will be enrolled to this phase II single-centre trial (n = 20). All pts undergo complete nodal resection (RES) at wk 6 following neo-adj therapy with pembrolizumab (200mg, IV, 3 wkly) and lenvatinib (20mg, oral, daily). Adjuvant therapy with pembrolizumab is given for 46 wks after RES. After 52 wks of the study treatment, pts will be followed for relapse and survival for 5 years. CT and FDG PET/CT are used to measure response and exclude progression in the neo-adj phase, and to monitor for recurrence during adj and post treatment phases. Blood and tumour samples are collected at baseline, day 8, RES and at relapse if feasible. Faecal samples are collected at baseline and before RES. The primary endpoint is the complete pathological response rate at RES following 6 wks of neo-adj therapy. Secondary endpoints include RECIST response, metabolic response, OS, RFS, safety/tolerability, surgical outcomes, quality of life, and biomarker analyses. Clinical trial information: NCTNCT04207086. Research Sponsor: Melanoma Institute Australia and Merck.

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**TPS10089** **Poster Session (Board #438), Fri, 8:00 AM-11:00 AM**

## Phase II single-arm multi-center study of adjuvant ipilimumab in combination with nivolumab in subjects with high-risk ocular melanoma.

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**Background:** Treatment of primary ocular melanoma is often very effective, with local recurrence rates of $< 5\%$. However, distant recurrence is as high as 50% depending on features of the primary tumor. These data emphasize the need for effective adjuvant therapy for patients with locally treated ocular melanoma. Several adjuvant treatments have been developed for patients with high-risk cutaneous melanoma, including ipilimumab and nivolumab monotherapies and an ongoing trial is exploring the nivolumab/ipilimumab combination (CA209-915), but patients with high-risk ocular melanomas have been excluded from these trials. As yet there is no approved adjuvant treatment for high-risk ocular melanoma patients. **Methods:** We are conducting a Phase II single-arm multi-center study of adjuvant ipilimumab in combination with nivolumab in subjects with high-risk ocular melanoma. This study aims to generate efficacy and safety data for adjuvant this regimen in patients with locally treated high-risk ocular melanoma with 3-year risk of relapse $> 50\%$. The primary endpoint is 3-year relapse-free survival rate. Secondary endpoints are median relapse-free survival, median overall survival, 3-year overall survival rate and safety. All patients will receive nivolumab 240mg IV every 2 weeks plus ipilimumab 1mg/kg IV every 6 weeks. Subjects may receive up to 25 doses of nivolumab and 8 doses of ipilimumab. The accrual goal is 50 patients across all participating institutions. Subjects treated in this study will be matched with controls selected from a contemporaneously collected OM registry, "contemporaneous control" in order to better assess efficacy. Control subjects will be from institutions not participating in this trial, will otherwise meet the trial eligibility criteria and will be further matched with trial participants for various demographic and risk factors to the extent possible. The study is enrolling in 6 comprehensive cancer centers in the US. Clinical trial information: NCT3528408. Research Sponsor: Bristol-Myers Squibb.

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**TPS10090** **Poster Session (Board #439), Fri, 8:00 AM-11:00 AM**

## S1801: A randomized phase II trial of adjuvant versus neoadjuvant pembrolizumab (PEM) for melanoma.

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**Background:** Although long term outcomes for most patients with early-stage melanoma is excellent following surgery, patients who have high-risk features such as lymph node involvement have poorer outcomes. Adjuvant therapy (AT) is currently considered for patients with stage III melanoma and selected patients with resected stage IV melanoma. Currently, AT for melanoma is anti-PD-1 or targeted therapy in the presence of a BRAF mutation. At this time we are not able to predict which patients will derive benefit from AT and experience cure. While curative surgery is the goal of early treatment of primary melanoma, some cases with bulky nodal involvement are at high risk of local or distant recurrence despite upfront surgery. Neoadjuvant treatment (NAT) offers the benefit of an early on-treatment pathological sample that can be profiled for biomarkers and correlated with survival. Treating with anti-PD1 while tumor transiently remains in the body may generate a stronger immune response from tumor-infiltrating lymphocytes against *in vivo* tumor antigens compared to the traditional adjuvant setting where antigen is presented by microscopic residual tumor burden. Pilot studies using NAT with have been initiated in melanoma. Multidisciplinary coordination in these cases is paramount. In these studies, an improvement in relapse-free survival and overall survival has been observed; additionally, pathologic response rates to NAT have been estimated in small studies. **Methods:** S1801 is a randomized phase II study of AT versus NAT with PEM (NCT03698019). Patients with measurable, clinically detectable and resectable cutaneous, acral, and mucosal melanomas without brain metastasis are eligible. Patients are randomized 1:1 to the AT or the NAT. Patients getting AT receive surgery first followed by 18 doses of PEM 200 mg IV every 3 weeks. Patients getting NAT receive 3 doses of pre-operative PEM followed by surgery and then 15 doses of adjuvant PEM. Radiation may be given on either arm after surgery, at the investigator's discretion. Primary endpoint is event-free survival measured from the date of randomization to the date of first documented progression that renders the patient unable to receive planned protocol surgery, failure to begin AT within 84 days of surgery, relapse after surgery, or death due to any cause. Safety monitoring is conducted with disease progression and toxicity thresholds. The key Translational Medicine objective of this trial is to determine the pathologic response rate to NAT with 3 doses of PEM. Enrollment is at 94 of a planned 500 patients. Clinical trial information: NCT03698019. Research Sponsor: U.S. National Institutes of Health.

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