9501 **Oral Abstract Session**

Significant durable response with fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: Post adjuvant PD-1 analysis.

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Background: Previous reports have demonstrated that treatment (Tx) with anti-LAG-3 Ab fianlimab + anti-PD-1 Ab cemiplimab had a 63.8% ORR across two separate cohorts of advanced PD-(L)1 naïve metastatic melanoma (Mel) patients (pts). The benefit the fianlimab + cemiplimab combination in pts exposed to prior anti-PD-1 Tx as adjuvant (adj) Tx is unknown. Here we present phase 1 safety and clinical activity data from pts with advanced Mel including those who received prior adj systemic Tx. **Methods:** Three separate expansion cohorts of adult pts with unresectable or metastatic Mel (excluding uveal Mel) who were anti–PD-(L)1 Tx-naïve for advanced disease were enrolled. All pts received fianlimab 1600 mg + cemiplimab 350 mg IV Q3W for 12 months (mos) (optional additional 12 mos if clinically indicated). Study enrollment closed in June 2022. Tumor measurements were performed every 6 weeks (wks) for 24 wks, then every 9 wks. **Results:** 98 pts were enrolled and treated with fianlimab + cemiplimab as of 01 Nov 2022 data cutoff. Median age was 68.0 years, 60.2% were male, and 89.8% were White. 2.0% of pts had received prior metastatic Tx (not anti–PD-(L)1) and 23.5% had received prior systemic Tx for Mel in the adj/neo-adj setting (disease-free interval $>$ 6 mos), including 13.3% treated with an anti-PD-1 (nivolumab or pembrolizumab). Median follow up was 12.6 mos and median treatment duration was 32.9 wks. Grade $\geq$3 treatment-emergent adverse events (TEAEs), serious TEAEs, and immune-related AEs (irAEs) occurred in 43.9%, 32.7%, and 65.3% of pts, respectively. 16.3% of pts discontinued Tx due to a TEAE. Rates of irAEs were similar to anticipated rates for PD-1 monotherapy with the exception of adrenal insufficiency (AI) with 12.2% (all grades) and 4.1% (grade $\geq$3). RECIST 1.1-based investigator-assessed overall ORR was 61.2% (12 complete responses; 48 partial responses), with median DOR (mDOR) not reached [NR] (95% CI: 22.6– not estimated [NE]). KM estimation of median PFS (mPFS) was 15.3 (95% CI: 9.4–NE) mos. In pts with any prior adj Tx, ORR, mDOR, and mPFS was 60.9% (14/23), NR, and 13.3 mos, respectively. In pts with prior anti-PD-1 adj Tx, ORR, mDOR, and mPFS was 61.5% (8/13), NR, and 11.8 mos, respectively. Data from subgroup and correlative biomarker analyses, PK and immunogenicity will be included in the presentation. **Conclusions:** Fianlimab + cemiplimab in advanced Mel pts showed high clinical activity that compares favorably with other approved combinations of immune checkpoint inhibitors in the same clinical setting. This is the first indication that dual LAG-3 blockade can produce high level of activity with significant ORR in pts with advanced Mel post adj anti-PD-1 Tx. The safety profile of fianlimab + cemiplimab is similar to anti-PD-1 monotherapy with the exception of AI. A phase 3 trial (NCT05352672) of fianlimab + cemiplimab in Tx-naïve advanced Mel pts is ongoing. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

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Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047.

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Background: In RELATIVITY-047 (NCT03470922), NIVO + RELA demonstrated a statistically significant progression-free survival (PFS) benefit vs NIVO; there was an observed improvement in overall survival (OS) although it was not statistically significant. The combination also had a descriptively higher confirmed objective response rate (ORR) assessed by blinded independent central review (BICR) vs NIVO. Here we report updated descriptive analyses (efficacy, safety, and secondary analyses) with longer (~ 2 years) follow-up. **Methods:** Patients were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg fixed-dose combination or NIVO 480 mg every 4 weeks, as previously described. Primary endpoint of PFS per RECIST v1.1 was assessed by BICR; secondary endpoints included OS and ORR per BICR. Exploratory analyses were performed for melanoma-specific survival (MSS; defined as death due to melanoma, with censoring of deaths due to other causes) and efficacy outcomes on subsequent systemic therapy. **Results:** Patients received NIVO + RELA (n = 355) or NIVO (n = 359). Median follow-up was 25.3 months in this updated analysis (minimum follow-up, 21.0 months). NIVO + RELA continued to show a benefit over NIVO for PFS, OS and ORR (Table). A similar improvement was also observed in MSS. NIVO + RELA was generally favored over NIVO across key subgroups (consistent with previous reports). Subsequent systemic therapy was received by 131 (36.9%) and 136 (37.9%) patients in the NIVO + RELA and NIVO arms, respectively. Treatment-related adverse events (TRAEs; any grade) leading to treatment discontinuation were observed in 61 (17.2%) and 31 (8.6%) patients on NIVO + RELA and NIVO, respectively. Grade 3–4 TRAEs were observed in 78 (22.0%) patients on NIVO + RELA and 43 (12.0%) patients on NIVO. In total, there were 6 treatment-related deaths (NIVO + RELA, n = 4; NIVO, n = 2); no new treatment-related deaths have been reported since the last analysis. **Conclusions:** With 12.3 months of additional follow-up, a consistent benefit was observed with NIVO + RELA vs NIVO for PFS, OS and ORR in the ITT population, as well as in key patient subgroups. MSS was longer with NIVO + RELA compared with NIVO. The safety profile of NIVO + RELA remained consistent with previous reports, with no new or unexpected safety signals. Efficacy outcomes on subsequent systemic therapy (by type of subsequent therapy, including PD-L1/CTLA-4) will be presented. Clinical trial information: NCT03470922. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, months (95% CI)	10.2 (6.5–14.8)	4.6 (3.5–6.5)
HR (95% CI)	0.81 (0.67–0.97)	
Median OS, months (95% CI)	NR (31.5–NR)	33.2 (25.2–45.8)
HR (95% CI)	0.82 (0.67–1.02)	
OS rate, % (95% CI)		
24 months	61.8 (56.5–66.6)	58.3 (52.9–63.2)
36 months	54.1 (48.6–59.3)	48.4 (42.9–53.8)
48 months	51.5 (45.9–56.9)	42.5 (36.4–48.5)
ORR, % (95% CI)	43.7 (38.4–49.0)	33.7 (28.8–38.9)
Median MSS, months (95% CI)	NR (NR–NR)	46.6 (33.2–NR)
HR (95% CI)	0.77 (0.61–0.97)	

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LBA9503 **Oral Abstract Session**

Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/ KEYNOTE-942 trial.

Adnan Khattak, Jeffrey S. Weber, Tarek Meniawy, Matthew H. Taylor, George Ansstas, Kevin B. Kim, Meredith McKean, Georgina V. Long, Ryan J. Sullivan, Mark B Faries, Thuy Tran, Charles Lance Cowey, Theresa Michelle Medina, Jennifer Margaret Segar, Victoria Atkinson, Geoffrey Thomas Gibney, Jason J. Luke, Elizabeth Iannotti Buchbinder, Robert S. Meehan, Matteo S. Carlino, on behalf of Moderna Author's Group; One Clinical Research and Edith Cowan University, Perth, Western Australia, Australia; Laura and Isaac Perlmutter Cancer Center, NYU School of Medicine, New York, NY; Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia; Earle A. Chiles Research Institute, Portland, OR; Washington University Oncology, St. Louis, MO; California Pacific Medical Center Research Institute, San Francisco, CA; Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; The University of Sydney, Sydney, NSW, Australia; Massachusetts General Hospital, Boston, MA; The Angeles Clinic and Research Institute, Los Angeles, CA; Yale-New Haven Hospital, New Haven, CT; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; University of Colorado, Aurora, CO; The University of Arizona Cancer Center, Tucson, AZ; Princess Alexandra Hospital and University of Queensland, Woolloongabba, QLD, Australia; Georgetown - Lombardi Comprehensive Cancer Center, Washington, DC; UPMC Hillman Cancer Center, Pittsburgh, PA; Dana-Farber Cancer Institute, Boston, MA; Moderna Therapeutics, Cambridge, MA; Melanoma Institute Australia, The University of Sydney, Westmead and Blacktown Hospitals, Sydney, Australia

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Association of biomarkers (BMs) with efficacy of adjuvant nivolumab (NIVO) vs placebo (PBO) in patients with resected stage IIB/C melanoma (CA209-76K).

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Background: Adjuvant NIVO significantly prolonged recurrence-free survival (RFS) over PBO in stage IIB/C melanoma in the randomized, phase III Checkmate 76K trial (HR; 95% CI: 0.42 [0.30–0.59]). For the first time, select BMs and their association with RFS were analyzed in early-stage melanoma treated with an anti-PD-1 agent. **Methods:** Baseline primary tumor and serum BMs were analyzed, including interferon gamma-related gene expression signature (IFNγ-sig), TMB, *BRAF* mutation, % intratumoral CD8+ T cells, tumor cell PD-L1 expression, and serum CRP levels. BMs were evaluated as continuous variables (high vs low levels) and dichotomized by median or prespecified cutoffs. HRs were estimated using a Cox proportional hazards model. **Results:** Analysis of continuous BM levels within treatment arms showed that higher IFNγ-sig, TMB, and % CD8+ T cells, and lower CRP levels were associated with prolonged RFS with NIVO but not PBO. The same trend was observed in the dichotomized analyses. No clear association between PD-L1 expression and RFS was identified in either arm. Benefit of NIVO over PBO was seen across all BM subgroups, including by $BRAF^{V600}$ mutation status. Patients with higher IFNγ-sig, TMB, and % CD8+ T cells, and lower CRP levels showed numerically greater relative benefit with NIVO, although CIs overlapped (Table). **Conclusions:** Higher IFNγ-sig, TMB, and % CD8+ T cells, and lower CRP levels were associated with longer RFS with NIVO treatment. No BMs assessed were prognostic for RFS in the PBO arm, in contrast to previous reports in melanoma. Prolonged RFS was seen in patients treated with NIVO over PBO across levels of BMs, and irrespective of *BRAF* mutational status. Composite analyses of BMs with clinical and histopathologic factors will be evaluated for their potential to optimize risk:benefit stratification for NIVO in this patient population. Clinical trial information: NCT04099251. Research Sponsor: Bristol Myers Squibb.

Association between biomarker levels and RFS (unstratified HR[a]).

	NIVO (within arm) [526]	PBO (within arm) [264]	NIVO vs PBO arms (BM high)	NIVO vs PBO arms (BM low)
IFNγ-sig[b]	0.59 (0.41, 0.86) [425]	0.91 (0.65, 1.27) [213]	0.29 (0.17, 0.48)	0.44 (0.29, 0.66)
TMB, log_{10} scale[b]	0.66 (0.49, 0.90) [441]	1.20 (0.89, 1.61) [217]	0.27 (0.17, 0.44)	0.50 (0.33. 0.74)
CD8+ T cells, %[b]	0.60 (0.39, 0.90) [464]	0.97 (0.71, 1.33) [243]	0.35 (0.22, 0.55)	0.56 (0.36, 0.87)
PD-L1, % TC[b]	0.82 (0.60, 1.12) [189]	0.99 (0.87, 1.12) [111]	0.43 (0.24, 0.76)	0.52 (0.28, 0.94)
CRP, log_2 scale, μg/mL[b]	1.37 (1.00, 1.88) [493]	0.92 (0.69, 1.24) [246]	0.50 (0.34, 0.74)	0.34 (0.22, 0.52)
$BRAF^{V600X}$ [c]	Mut vs WT 1.41 (0.82, 2.43) [441]	Mut vs WT 0.78 (0.45, 1.35) [217]	Mut 0.56 (0.30, 1.04)[c]	WT 0.33 (0.21, 0.53)

[a]Continuous HR: high biomarker level over low level from Cox proportional hazards model with arms; (95% CI) [N], except BRAF. [b]Continuous: higher vs lower. [c]$BRAF^{V600X}$ mutation detected (Mut) vs not detected (wild-type; WT).

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LBA9505 **Oral Abstract Session**

Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the phase 3 KEYNOTE-716 study.

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Non-comparative, open-label, international, multicenter phase I/II study of nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with recurrent/metastatic merkel cell carcinoma (MCC) (CheckMate 358).

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Background: MCC is a rare and aggressive skin cancer. Programmed death-ligand 1 (PD-L1) is often upregulated in MCC and blockade of PD-L1 or its receptor, PD-1, has improved survival for patients with metastatic MCC. Anti–PD-1 combined with anti–CTLA-4 has been reported to improve outcomes over anti–PD-1 monotherapy (NCT03071406; Kim S et al., *Lancet* 2022), however further investigation is needed. CheckMate 358 (NCT02488759) assessed NIVO ± IPI in 2 non-randomized MCC cohorts. **Methods:** Eligible pts had recurrent or metastatic MCC, ≤ 2 prior therapies, ECOG performance status (PS) 0–1, and no prior immune checkpoint inhibitor (ICI) therapy. Pts were eligible regardless of PD-(L) 1 status. Pts received NIVO 240 mg Q2W or NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W for ≤ 24 months (m) or until disease progression, unacceptable toxicity, or consent withdrawal. Imaging was conducted Q8W in year 1 and Q12W thereafter. Planned sample sizes were 23 pts for NIVO and 40 pts for NIVO + IPI. The primary endpoint was investigator-assessed objective response rate (ORR). Secondary endpoints included duration of response (DOR), investigator-assessed progression-free survival (PFS), and overall survival (OS). **Results:** 68 pts received NIVO (n = 25) or NIVO + IPI (n = 43) with ≥ 24 m follow-up (median: NIVO, 62.5 m; NIVO + IPI, 24.4 m). In the NIVO arm, median age was 66 yrs (range, 27–88), 10 (40.0%) pts had ECOG PS of 1, and 15 (60.0%) were treatment-naive. In the NIVO + IPI arm, median age was 70 yrs (range, 48–85), 27 (62.8%) pts had ECOG PS of 1, and 33 (76.7%) were treatment-naive. Treatment duration was 15.8 m in the NIVO arm, and 7.9 m for NIVO and 6.0 m for IPI in the NIVO + IPI arm. Efficacy and safety outcomes are summarized in the table. ORR was 60.0% (95% CI, 38.7–78.9) in the NIVO arm and 58.1% (95% CI, 42.1–73.0) in the NIVO + IPI arm. The most common reasons for treatment discontinuation were disease progression (NIVO, 28.0%; NIVO + IPI, 32.6%) or study-drug toxicity (NIVO, 20.0%; NIVO + IPI, 25.6%). There was 1 study drug-related death in each arm (NIVO, pneumonitis; NIVO + IPI, gastrointestinal motility disorder). **Conclusions:** Both NIVO and NIVO + IPI show durable clinical efficacy in advanced MCC. While the non-randomized trial design limits comparisons between the arms, results do not suggest additional efficacy benefit with IPI added to NIVO. Higher incidence of grade 3/4 TRAEs observed in the combination arm could have resulted in shorter treatment duration. Clinical trial information: NCT02488759. Research Sponsor: Bristol Myers Squibb.

	NIVO (n = 25)	NIVO + IPI (n = 43)
ORR, n (% [95% CI])	15 (60.0 [38.7–78.9])	25 (58.1 [42.1–73.0])
Complete response, n (%)	8 (32.0)	8 (18.6)
Partial response, n (%)	7 (28.0)	17 (39.5)
Median DOR, m (95% CI)	60.6 (16.7–NA)	25.9 (10.4–NA)
Median PFS, m (95% CI)	21.3 (9.2–62.5)	8.4 (3.7–24.3)
Median OS, m (95% CI)	80.7 (23.3–NA)	29.8 (8.5–48.3)
Any-grade/grade 3/4 TRAE, %	84.0/28.0	83.7/46.5

NA, not applicable.

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9507 **Oral Abstract Session**

Towards organ preservation and cure via 2 infusions of immunotherapy only, in patients normally undergoing extensive and mutilating curative surgery for cutaneous squamous cell carcinoma: An investigator-initiated randomized phase II trial—The MATISSE trial.

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Background: Standard of care for locally advanced cutaneous SCC (CSCC) consists of extensive and mutilating surgery often with adjuvant radiotherapy (RT). To improve clinical prospects of these patients (pts), we tested efficacy of neoadjuvant nivolumab (NIVO) and nivolumab plus ipilimumab (COMBO) in pts with CSCC with an indication for extensive surgery with or without adjuvant RT. **Methods:** 40 pts with T1-4N0-3M0 or TxN1-3M0 CSCC and an indication for extensive and/or mutilating surgery were needed to reach the primary objective of this trial. Pts were randomized for ARM A: NIVO (3 mg/kg, weeks 0&2, N = 26) or ARM B: NIVO (3 mg/kg, weeks 0&2) + IPI (1mg/kg, week 0, N = 24) prior to surgery (week 4). Primary objective was pathological response at time of surgery. A major pathological response (MPR) was defined as $\leq$10% residual viable cancer cells in the surgical resection specimen. Secondary endpoints were tolerability (CTCAE v.5.0), survival, and quality of life (QOL). Key exploratory aim for the trial was the serial collection of pre- and on-treatment tumor samples to investigate immunogenomic features correlating with immunotherapy response. **Preliminary results:** 50 pts were enrolled at median age 76, of whom 32% with TxN1-3M0 disease. Grade 3-4 irAEs occurred in 6 (12%) pts and were well manageable. 40 pts underwent standard of care surgery w/wo adjuvant RT, of whom 40% and 53% reached an MPR upon NIVO and COMBO, respectively. However, 10 pts withdrew consent to undergo surgery and RT, of whom nine pts declined because of self-reported substantial clinical remission upon neoadjuvant immunotherapy. These clinical responses were confirmed via FDG-PET evaluation in week 4. All these 9 pts are currently cancer free at median FU of 12 months (range 4 to 27) with superior QOL compared to MATISSE pts undergoing standard of care. Overall, we found deep clinical responses in 13/26 (50%) and 14/23 (61%) of pts upon NIVO and COMBO, respectively, being either a MPR at time of surgery or a clinical CR in patients declining surgery. **Preliminary conclusions:** The MATISSE trial shows deep responses of 50% and 61% upon neoadjuvant NIVO and COMBO, respectively, with well manageable toxicity in this elderly CSCC population. Nine MATISSE patients have proven the concept that organ preservation and durable complete remissions can be achieved after two infusions of neoadjuvant immunotherapy only, without extensive or mutilating curative surgery and/or RT. Clinical trial information: NCT04620200. Research Sponsor: The MATISSE trial is an investigator-initiated randomized phase II trial, partly funded by Bristol-Myers Squibb; Riki Foundation (private foundation).

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9508 **Oral Abstract Session**

Temozolomide plus cisplatin versus toripalimab (anti-PD-1) as adjuvant therapy in resected mucosal melanoma.

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Background: Chemotherapy (temozolomide plus cisplatin) has been demonstrated to be a better adjuvant regimen compared to high-dose interferon alpha-2b in resected Mucosal Melanoma (MuM) in the pre-immunotherapy era. Yet in the present immunotherapy era, PD-1 inhibitor was recommended as a standard adjuvant therapy for resected Melanoma. No adjuvant trial comparing chemotherapy with PD-1 inhibitor in resected MuM had been reported. we conducted this study to determine the efficacies of adjuvant chemotherapy versus PD-1 inhibitor in resected MuM. **Methods:** All patients (pts) with resected MuM received chemotherapy (temozolomide 200 mg/m^2/day orally on days 1 to 5 plus cisplatin 75 mg/m^2 i.v. on days 1-3, repeated every 3 weeks for six cycles) or Toripalimab (anti-PD-1, 3 mg/kg every 2 weeks via intravenous infusion) as adjuvant therapy from 2013 to 2019 were included retrospectively. Demographic and clinical characteristics between the two groups were matched with 1:1 by propensity score matching (PSM) to reduce the bias. After PSM, the efficacies of the two groups were compared, and subgroup analysis was performed according to the baseline characteristics. The endpoints were relapse-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS). Kaplan-Meier methods and Cox regressions were used to estimate median RFS, DMFS, OS and HR. **Results:** A total of 247 pts were included, of which 78 were in the Toripalimab group and 169 were in the Chemo group. PSM matched 65 pts from each of the two groups. The baseline characteristics were similar. At a median follow-up of 52.6 months (95%CI, 44.6-60.6 months), patients receiving chemo had a longer median RFS (28.2 vs. 12.0 months; HR=0.64, 95% CI, 0.42 to 0.98; P=0.04), DMFS (42.0 vs. 19.0 months; HR=0.58, 95% CI, 0.36 to 0.92; P=0.02) and OS (93.4 vs. 39.3 months; HR=0.56, 95% CI, 0.33 to 0.94; P=0.03) versus the toripalimab group (Table). **Conclusions:** Adjuvant chemotherapy (temozolomide plus cisplatin) shows remarkable longer RFS, DMFS, and OS than Toripalimab (anti-PD-1). It suggested that adjuvant chemotherapy may be a better option for patients with resected mucosal melanoma even in the present immunotherapy era. Research Sponsor: None.

Characteristics and efficacies of two groups after PSM.

	Chemo (N = 65)	Anti-PD-1 (N = 65)	P value	HR (Chemo vs anti-PD-1)
Age in years, median (range)	59.0 (33.0-80.0)	60.0 (38.0-74.0)	0.43	
Sex, male, n (%)	29 (44.6)	22 (33.8)	0.21	
Primary site, Head and neck, n (%)	24 (36.9)	25 (38.5)	0.86	
LN metastasis, yes, n (%)	15 (23.1)	15 (23.1)	/	
ECOG ≤1, n (%)	65 (100)	65 (100)	/	
NLR ≤3, n (%)	55(84.6)	57(87.7)	0.61	
Median RFS, mo.(95% CI)	28.2 (17.7 - 38.7)	12.0 (7.1 - 16.9)	0.04	0.64 (0.42 - 0.98)
Median DMFS, mo.(95% CI)	42.0 (NA)	19.0 (11.6 - 26.4)	0.02	0.58 (0.36 - 0.92)
Median OS, mo.(95% CI)	93.4 (31.6 - 155.2)	39.3 (26.2 - 52.4)	0.03	0.56 (0.33 - 0.94)

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Initial efficacy and safety of RP1 + nivolumab in patients with anti–PD-1–failed melanoma from the ongoing phase 1/2 IGNYTE study.

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Background: Patients (pts) with melanoma who progress on anti–PD-1 therapy (anti–PD-1–failed) have limited treatment options. RP1 is an HSV-1–based oncolytic immunotherapy expressing human GM-CSF and a fusogenic protein (GALV-GP-R−). Here, we present data from the first 75 pts enrolled into the registration-directed (R-D) cohort in anti–PD-1–failed melanoma (target enrollment N = 125) from the phase 1/2 IGNYTE study (NCT03767348). **Methods:** Pts must have locally advanced or metastatic cutaneous melanoma with ≥1 measurable and injectable tumor (≥1 cm) and confirmed progressive disease (PD) on 2 assessments ≥28 days apart while on ≥8 consecutive weeks of anti–PD-1 ± anti–CTLA-4 therapy, with anti–PD-1 being the last treatment received. Pts on prior adjuvant anti–PD-1 therapy must have had PD confirmed by biopsy while on adjuvant therapy. RP1 is initially given intratumorally at 10^6 PFU/mL and then every 2 weeks (Q2W) at 10^7 PFU/mL for ≤8 total cycles (≤10 mL/dose) combined with nivolumab (nivo; cycles 2–8, 240 mg IV); pts then receive nivo alone (240 mg Q2W or 480 mg Q4W IV) for ≤2 years, with the option to reinitiate RP1 if specified criteria are met. **Results:** A total of 91 pts are included in this analysis (initial melanoma cohort, 16 pts; R-D cohort, 75 pts; data cut: Dec 30, 2022). The overall objective response rate (ORR) was 37.4% (initial cohort, 37.5%; R-D cohort, 37.3%) and 18.7% of pts achieved complete response (CR; Table). The response rates seen were also encouraging when evaluated by prior anti–PD-1 therapy setting and disease stage (Table). Responses were seen in uninjected lesions in most responding patients, including in pts with bulky and visceral disease. The majority of responses were observed in pts with PD-L1–negative tumors at baseline (17 of 52 pts with PD-L1–negative tumors responded, compared to 15 of 26 pts with PD-L1–positive tumors, and 2 of 13 pts for whom PD-L1 status was unknown). 85.3% of responses were ongoing 3.7–36.6 months from initiating therapy. Most treatment-related adverse events (TRAEs) were Grade 1–2 with the most common (>20%) being fatigue, chills, pyrexia, and nausea. **Conclusions:** The initial data from this expanded cohort show that RP1 + nivo provides durable and clinically meaningful antitumor activity in pts with anti–PD-1–failed melanoma. Responses were observed in both injected and uninjected lesions, including visceral lesions. The combination continues to be well tolerated, with mostly on-target TRAEs. Additional and updated data will be presented. Clinical trial information: NCT03767348. Research Sponsor: Replimune Inc.

IGNYTE response data[a].

	Pts N	CR n (%)	ORR n (%)
All pts	91	17 (18.7)	34 (37.4)
Initial cohort	16	2 (12.5)	6 (37.5)
R-D cohort	75	15 (20.0)	28 (37.3)
Prior anti–PD-1	30	9 (30.0)	15 (50.0)
Adjuvant	61	8 (13.1)	19 (31.1)
Non-adjuvant	31	2 (6.3)	10 (32.3)
Anti–PD-1 + anti–CTLA-4			
Stage	45	13 (28.3)	21 (46.7)
IIIb–IVa	46	4 (8.7)	13 (28.3)
IVb–IVc			

[a]Investigator-assessed responses.

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9510 **Poster Discussion Session**

Efficacy and safety of tunlametinib in patients with advanced NRAS-mutant melanoma: A multicenter, open-label, single-arm, phase 2 study.

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Background: NRAS-mutant melanoma is an aggressive subtype with worse prognosis. However, no targeted therapy has been approved to date worldwide. Tunlametinib (HL-085), a novel, potent, selective, oral small-molecule MEK1/2 inhibitor, has showed a favorable pharmacokinetics profile, acceptable tolerability and encouraging antitumor activity in the phase 1 study (BMC Med. 2023 Jan 4;21(1):2). **Methods:** This is an ongoing, multicenter, open-label, single-arm, phase 2 pivotal registration study. Patients (pts) with NRAS-mutant unresectable stage III or IV melanoma were enrolled and received tunlametinib 12 mg orally twice daily. A historical control of objective response rate (ORR) of 10% was predefined for sample size estimation (100 pts, assuming loss to follow-up rate of 5%) and efficacy evaluation. The primary endpoint was the confirmed ORR per RECIST v1.1 assessed by independent radiology review committee. **Results:** A total of 100 pts were enrolled. All pts were included in the safety analysis set and 95 pts were included in the full analysis set (FAS) for efficacy analysis. At cut-off date (August 17, 2022), median follow-up was 7.9 months (95% CI: 6.6, 9.8). In the FAS, the median age was 58.0 years (range: 24 to 84). Sixty-four pts (67.4%) had received prior immunotherapy (PD-1/PD-L1 inhibitor). Fifty-six pts (58.9%) were acral melanoma, 16 (16.8%) mucosal melanoma and 12 (12.6%) skin melanoma. Fourteen pts (14.7%) were stage III and 81 (85.3%) stage IV. The most frequent NRAS mutation types were Q61R (40.0%), Q61K (29.5%) and G12D (9.5%). Confirmed ORR was 34.7% (95%CI: 25.3%, 45.2%). Median progression-free survival was 4.2 months (95%CI: 3.5, 5.6), overall survival was immature, and 1-year survival rates was 57.2% (95% CI, 44.7%, 67.8%). Subgroup analysis showed that, in pts who had previously received immunotherapy, the confirmed ORR was 39.1% (95% CI: 27.1%, 52.1%). The most frequent treatment related adverse events (TRAEs) were increased blood creatine phosphokinase (CK), diarrhea, peripheral oedema, facial oedema and increased aspartate aminotransferase. Grade ≥3 TRAEs occurred in 68 pts (68.0%), of which 38.0% (38/100) were increased blood CK. Most of pts with CK elevation are asymptomatic and can be managed by dose interruption or reduction without permanent treatment discontinuation. No treatment-related death was reported. **Conclusions:** Tunlametinib was well tolerated and demonstrated encouraging treatment response rate in pts with advanced NRAS-mutant melanoma. These results indicate that tunlametinib could be a promising treatment option for NRAS-mutant melanoma, even for those immunotherapy failed pts. Clinical trial information: NCT05217303. Research Sponsor: Shanghai KeChow Pharma.

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9511 **Oral Abstract Session**

Randomized phase II trial of dabrafenib and trametinib with or without navitoclax in patients (pts) with BRAF-mutant (MT) metastatic melanoma (MM) (CTEP P9466).

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Background: Standard MAPK-targeted therapy (tx) for pts with BRAF MT MM involves combined BRAF and MEK inhibition with high efficacy in advanced melanoma, but durability of response is limited by acquired resistance. One combination, dabrafenib and trametinib (DT), was shown to be less effective in the frontline setting than combined immune checkpoint inhibition (ICI) but did achieve a 48% objective response rate (ORR) after ICI. (Atkins et al., JCO 2022) Preclinical data show that targeting mediators of apoptosis improves response and survival with BRAF-targeted tx. Navitoclax (N) is a BH3-mimetic that inhibits BCL-2, BCL-xL, and BCL-W. We previously demonstrated the safety of DTN in patients with BRAF MT solid tumors in a phase I trial. This randomized phase II study compared DTN to DT. (NCT01989585). **Methods:** Pts with BRAF MT MM were randomized 1:1 to either DT (standard dosing D 150 mg BID and T 2 mg QD) or DTN (standard DT plus N 225 mg QD) and stratified by maximal tumor burden (RECIST 1.1 sum of diameter of target lesions $\geq$ 100 mm or $<$ 100 mm). The target sample size was 50 evaluable pts (25 per arm). Prior ICI, but not prior BRAF targeted therapy, was permitted. The co-primary endpoints were to estimate complete response (CR) rate for DTN compared to historic controls and to assess maximal tumor shrinkage of pts treated with DTN vs DT. Secondary endpoints included ORR, progression-free survival (PFS) and overall survival (OS). **Results:** Fifty-six pts were enrolled and 50 treated (25 DTN, 25 DT) from 1/11/19 – 3/25/22 at 13 sites. Seventeen pts (68%) in each arm received prior ICI. The ORR was 84% for DTN and 80% for DT. The CR rate for DTN was 20% and 15% for DT; this met pre-specified criteria for success of the primary CR endpoint. There was no difference in the maximal tumor shrinkage in pts treated with DTN vs DT. With median follow up of 25.9 months (mo), there was a trend for improved OS with DTN vs DT (median 36 vs 25 mo, log-rank $p = 0.07$). In the stratification cohort of 37 pts (74%) with smaller baseline tumor burden, there was a statistically significant improvement in OS among pts receiving DTN (log-rank $p = 0.05$), with two-year estimates of OS of 78% (95% CI: 0.46 to 0.93) for DTN and 57% (95% CI: 0.29 to 0.77) for DT. There was no difference in PFS between the two groups. The most common treatment-related toxicities ($>$ 50% of pts) were nausea (36), diarrhea (31), fatigue (30), fever (28), and vomiting (27), which were not different in pts treated with DTN vs DT. **Conclusions:** In pts with BRAF MT MM, DTN was associated with a CR rate of 20% and ORR of 84%. There was a trend for improved OS in pts treated with DTN compared to DT; the difference in OS was significant in pts with smaller tumor burden. The DTN regimen may be considered for further exploration in the post-ICI setting. Updated data on survival and translational studies will be presented. Clinical trial information: NCT01989585. Research Sponsor: U.S. National Institutes of Health.

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LBA9512 **Poster Discussion Session**

Survival after isolated hepatic perfusion as a treatment for uveal melanoma liver metastases: Results from a randomized controlled trial (the SCANDIUM trial).

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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9513 **Poster Discussion Session**

Tumor infiltrating lymphocyte (TIL) harvest and ex vivo expansion from primary and metastatic (met) uveal melanoma (UM) tumors.

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Background: Adoptively transferred autologous cell therapy using tumor-infiltrating lymphocytes (TIL) is an emerging treatment for met melanoma. Responses have been seen in patients (pts) with checkpoint inhibitor-naïve and -refractory cutaneous melanoma. UM represents a disease subtype that is traditionally less responsive to immune checkpoint blockade (ICB). Preliminary studies have shown clinical utility of TIL in UM pts. However, data describing the success rates of TIL harvest and *ex vivo* expansion of cells from primary and met UM tumors, and of the treatment of pts with met UM, is limited. **Methods:** Between 2004 and 2019, we conducted a single-center IRB-approved trial (NCT NCT00338377) for TIL harvest in pts age 18 and older with documented met melanoma, including UM pts. The protocol was amended to allow harvest of primary UM tumors in 2015 if the pt was dispositioned for enucleation as primary treatment. **Results:** A total of 96 UM pts underwent TIL harvest; 9 underwent treatment with TIL. Median age was 54 years (range: 28 – 86); 56% of the pts were male; 78% were Caucasian, 9% Hispanic, and 13% unknown ethnicity. Overall successful *ex vivo* expansion of TIL occurred in 34.8% (32/92) of UM tumors in typical tumor fragment culture with IL-2 (TIL 1.0), with higher rates observed with UM mets (29/65; 44.6%) than UM primary tumors (3/27; 11.1%). Better results were observed with a culture method (TIL 3.0) that includes agonistic stimulation of CD3 and 41BB, with 96.8% (30/31 tumors). Expansion using this new method was successful in 9/10 primary UM tumors and 21/21 UM mets. Average number of days in culture for successful initial *ex vivo* expansion was 33.0 days for TIL 1.0 and 17.9 days for TIL 3.0 (p-value$<$0.0001). Overall, the average number of TIL expanded from culture and cryopreserved for clinical use was 130.4 million for TIL 1.0 (range: 34-460) and 326.2 million for TIL 3.0 (range 102-760) (p-value$<$0.0001). Nine met UM pts received treatment with up to 150 x 10^9 post-Rapid Expansion Protocol (REP) TIL (5 TIL 1.0, 4 TIL 3.0). Median age was 53, 44% were male, and all had active liver mets with a median of 3 lines of prior treatment for advanced disease. 8 of the TIL products were from UM mets (4 soft tissue, 3 liver, 1 combination of soft tissue and liver tumors), and 1 was from primary UM tumor, for which TIL could only be expanded with TIL 3.0. Best overall response rate per immune-related response criteria was 22% partial response (PR, duration of response was 22.1 months and 16.5 months), 44% stable disease (SD), and 33% progression of disease (PD) for a disease control rate of 66% (PR + SD). Both responding pts had TIL harvests from mets and had previously progressed on ICB, one was treated with TIL 3.0. **Conclusions:** TIL harvest and successful *ex vivo* expansion of cells is possible from both primary and met UM with TIL 3.0 culture method and can be therapeutically effective. Clinical trial information: NCT00338377. Research Sponsor: U.S. National Institutes of Health.

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9514 **Poster Discussion Session**

NeoPlus: A phase II study of neoadjuvant lenvatinib and pembrolizumab in resectable mucosal melanoma.

Lili Mao, Lu Si, Jie Dai, Xue Bai, Caili Li, Xiaoting Wei, Chuanliang Cui, Zhihong Chi, Xinan Sheng, Bixia Tang, Bin Lian, Xuan Wang, Xieqiao Yan, Li Zhou, Yan Kong, Xiaowen Wu, Siming Li, Juan Li, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology,Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education, Beijing), Department of Melanoma & Sarcoma,Peking University Cancer Hospital & Institute, Beijing, China

Background: Combination therapy of anti-PD1 agent with VEGFR inhibitor is a promising therapeutic approach in unresectable or metastatic mucosal melanoma. We conducted this study evaluating neoadjuvant lenvatinib and pembrolizumab in pts with resectable mucosal melanoma. **Methods:** This was a single-arm, open-label, single-center, ongoing phase 2 study conducted from Sep 2021. Eligible pts were adults (18-75 yr) with histologically confirmed, resectable mucosal melanoma. Pts received lenvatinib 20mg qd and pembrolizumab 200mg q3w for 2 cycles, followed by surgery. Pembrolizumab (200mg q3w) continued post operatively for further 15 cycles. The primary endpoint was complete pathologic response (pCR). Secondary endpoints were Event free survival (EFS), Overall survival (OS) and safety. **Results:** As of Dec 2022, 19 pts were enrolled with a median follow-up of 49 wks (95%CI, 38 -60). Median age was 57 yrs, 14 were female. Primary sites included: 8 female genital, 6 ano-rectal, 4 head & neck (1 nasal, 3 oral),1 esophageal. 12 pts were localized disease,7(37%) were regional lymphatic disease. KIT or NRAS mutations were presented in 2 and 3 pts, respectively. 15 pts underwent surgery, 2 pts had a pCR (13.3 %), 1 MPR, 3 pPR, with a pathologic response rate of 40%(6/15,95%CI 16-67%). 4 pts did not proceed with planned surgery for pts preference. Median EFS has not been reached. IHC data of the resected tumor showed higher CD8+ T cells density in responders (R=pCR+ MPR + pPR) than non-responders (NR=pNR) ($p = 0.04$). In 6 pts(one pPR and 5pNR) with paired pre and post treatment samples, CD3+ and CD8+ T cells were significantly increased following treatment ($p = 0.03$). Most common AEs were proteinuria (6, 32%), hypothyroidism (6, 32%), dysphonia (5, 26%). One pt(5%, 1/19) had grade 3 ALT elevation. No grade 4-5 toxicities were observed. **Conclusions:** The combination of pembrolizumab plus lenvatinib as neoadjuvant therapy in resectable MM is safe. The preliminary data has shown promising pathologic response with increased CD8+ T cell infiltration, supporting further investigation of neoadjuvant treatment in MM. Acknowledgement: Investigational funding and products are granted from Merck Sharp & Dohme LLC. Clinical trial information: NCT04622566. Research Sponsor: Merck Sharp & Dohme LLC; National Natural Science Foundation of China.

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LBA9515 **Poster Discussion Session**

Minimal residual disease by circulating tumor DNA as a biomarker of recurrence free survival in resected high-risk melanoma patients treated with mRNA-4157/V940, a personalized cancer vaccine, and pembrolizumab.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2023, issue of the *Journal of Clinical Oncology*.

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9516 **Poster Discussion Session**

Revisiting the optimal neoadjuvant immunotherapy regimen in resectable stage III melanoma based on the interferon gamma signature: A pooled analysis.

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Background: Neoadjuvant anti-PD1 has been shown to be superior to adjuvant administration. Combination of neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) induces even higher pathologic response rates (pRR) and event-free survival (EFS), but at the cost of higher toxicity. We previously showed that the interferon gamma (IFN-γ) signature is associated with a higher pRR after neoadjuvant IPI+NIVO. We hypothesized that IFN-γ high patients (pts) might benefit from less toxic anti-PD1 monotherapy (mono), while IFN-γ low pts might need an escalated regimen with IPI 3mg/kg + NIVO 1mg/kg. **Methods:** In this pooled analysis, pts with macroscopic nodal melanoma who received neoadjuvant NIVO 1mg/kg + IPI 3mg/kg (IPI3/NIVO1), IPI 1mg/kg + NIVO 3mg/kg (IPI1/NIVO3), sequential IPI 3mg/kg and NIVO 3mg/kg (IPI3>NIVO3), or NIVO mono (240mg; IFN-γ high pts only) from the OpACIN-neo, PRADO and DONIMI trials, were analyzed according to their baseline IFN-γ signature. RNA gene expression from baseline tumor biopsies was analyzed using the Nanostring nCounter platform. The IFN-γ scores were calculated using an algorithm and cut-off previously developed at the NKI and prospectively tested in the DONIMI trial. **Results:** Baseline tumor material was available from 151 pts (Table). Median follow-up was 42 months for the entire cohort and 19 months for NIVO mono pts. Combined IPI+NIVO in IFN-γ high pts induced similar major pathologic response (MPR) rates compared to NIVO mono in IFN-γ high pts (71% vs 80%, p=0.715), and significantly higher MPR rates compared to IPI+NIVO in IFN-γ low pts (71% vs 45%, p=0.003). At 18-months, EFS rates were 87%, 100% and 73% respectively, and overall survival (OS) rates were 98%, 100% and 96%. Notably, IPI3/NIVO1 seemed to induce a higher MPR rate than IPI1/NIVO3 in IFN-γ low pts (64% vs 41%), which was not statistically significant due to small subgroups. At 36 months, EFS was 91% vs 62% and OS was 91% vs 82%. **Conclusions:** Neoadjuvant NIVO mono seems to have equal outcomes as IPI+NIVO in IFN-γ high pts. IFN-γ low pts may benefit from IPI+NIVO with higher doses of IPI. Incorporating baseline biomarkers like the IFN-γ signature algorithm in neoadjuvant treatment decisions will optimize the risk-benefit ratio for these pts. Research Sponsor: BMS and 4SC.

IFN-γ score	Neoadjuvant regimen	No. pts	MPR (%)	EFS 18 months (%, 95% CI)	EFS 36 months (%, 95% CI)	OS 18 months (%, 95% CI)	OS 36 months (%, 95% CI)
High	**NIVO**	10	80	100	-	100	-
	IPI/NIVO	63	71*	87 (79-96)	83 (74-92)	98 (95-100)	92 (85-99)
	IPI1/NIVO3	46	74	91 (83-100)	85 (75-96)	100	96 (90-100)
	IPI3/NIVO1	9	78	78 (55-100)	78 (55-100)	89 (71-100)	78 (55-100)
	IPI3>NIVO3	8	43*	75 (50-100)	75 (50-100)	100	88 (67-100)
Low	**IPI/NIVO**	78	45	73 (64-84)	68 (58-79)	96 (92-100)	85 (77-93)
	IPI1/NIVO3	56	41	70 (59-83)	62 (51-77)	96 (92-100)	82 (73-93)
	IPI3/NIVO1	11	64	91 (75-100)	91 (75-100)	91 (75-100)	91 (75-100)
	IPI3>NIVO3	11	45	73 (51-100)	73 (51-100)	100	91 (75-100)

*1 patient not evaluable.

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9517 **Poster Discussion Session**

Final clinical results and first translational correlates of a phase 2 trial of adaptively dosed nivolumab and ipilimumab based on early radiographic assessment in advanced melanoma (ADAPT-IT).

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Background: Initial results from ADAPT-IT (NCT03122522) demonstrated that adaptive dosing of nivolumab (nivo) and ipilimumab (ipi) based on early radiographic assessment was associated with comparable response rates and toxicity compared to historical data for conventional nivo + ipi. Here, we report the final clinical analysis, including median progression-free survival (PFS), and present the first correlative analyses of blood-based biomarkers of response. **Methods:** ADAPT-IT was a multicenter, phase 2 clinical trial with a planned sample size of 60 patients with unresectable melanoma. Patients received two doses of nivo (1 mg/kg) + ipi (3 mg/kg) followed by a computed tomography scan at week 6. Patients with early favorable antitumor effect (FATE; defined as the absence of new lesions and $\leq$ 4% index lesion tumor growth), discontinued ipi and continued nivo alone. Patients without FATE at week 6 received third and fourth doses of nivo + ipi followed by nivo alone. The primary endpoint was investigator-assessed overall response rate (ORR; defined as the percent of patients with complete or partial responses by RECIST v1.1) at week 12. A Simon two-stage design was employed where a 43% 12-week ORR was considered not promising, a 60% 12-week ORR was considered promising, and the probabilities of type I and type II error were each set at 0.10. Pre- and on-treatment peripheral blood samples were assayed for 1) ten cytokines using a multiplex immunoassay (Meso Scale Diagnostics) and 2) circulating tumor DNA (ctDNA) using the MSK-ACCESS sequencing platform. The Wilcoxon rank sum test and Cox regression modeling were used to evaluate associations between biomarker levels with radiographic response and PFS, respectively. **Results:** 60 patients were enrolled. Week 12 and best ORR were 48% (95% CI, 35-61%) and 58% (95% CI, 45-71%), respectively. Median follow-up was 34 months (interquartile range: 21-36) in survivors, median PFS was 21 months (95% CI: 11-not reached) and the median overall survival was not reached. There were no new Grade 3-5 treatment-related adverse events since the initial report. Higher baseline IL-6 was observed in non-responders compared to responders ($p = 0.03$; $n = 26$) and was associated with shorter PFS (HR for progression or death 1.24; 95% CI: 1.01-1.52; $p = 0.04$). Among 20 patients with detectable ctDNA at baseline (of 25 patients with available samples), an increase in mean adjusted variant allele fraction from baseline to week 6 was associated with shorter PFS (HR 1.14; 95% CI: 1.02-1.27; $p = 0.02$). **Conclusions:** In this updated analysis, now with long-term follow-up, the efficacy of adaptively dosed nivo + ipi resembles that of historical data for standard dose nivo + ipi. Baseline IL-6 and on-treatment changes in ctDNA warrant further prospective study as biomarkers of response to ipi + nivo. Clinical trial information: NCT03122522. Research Sponsor: Bristol Myers Squibb.

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Efficacy of adjuvant therapy in patients (pts) with AJCC v8 stage IIIA cutaneous melanoma.

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Background: Pts with resected AJCC v8 stage IIIA melanoma have been under-represented in clinical trials of adjuvant drug therapy. The benefit of adjuvant targeted and immunotherapy in this population is unclear. **Methods:** In this multicenter, retrospective study, pts with stage IIIA melanoma (AJCC v8) who received adjuvant pembrolizumab or nivolumab (PD1), BRAF/MEK-targeted therapy dabrafenib + trametinib (TT), or no adjuvant treatment (OBS) were included. Recurrence free survival (RFS), distant metastasis free survival (DMFS), and toxicity rates were examined. **Results:** 613 pts from 34 centers across Australia, Europe and USA were included. The median follow-up was 2.6 yrs (IQR, 1.6-3.4 yrs). Pt characteristics and follow-up were similar across the cohorts (Table). Completion rates of 12-month PD1 and TT therapy were 57.0% and 69.2% respectively. 1-yr RFS was 93.3% (95% CI, 90.3-96.4) in PD1, 100% in TT and 91.3% (95% CI, 88.1-94.7) in OBS cohorts. 2-yr RFS was 79.3% (95% CI, 74.1-84.8) for PD1, 100% for TT and 84.3% (95% CI, 79.9-89.0) in OBS cohorts. 2-yr DMFS was 88.4% (95% CI, 84.3-92.8) in PD1, 100% in TT and 91.1% (95% CI, 87.7-94.7) in OBS cohorts. Risk of recurrence was associated with higher breslow thickness (HR 1.73, 95% CI 1.36-2.20), higher mitotic rate (HR 1.07, 95% CI 1.02-1.12) and neck as the site of nodal metastases (HR 2.71, 95% CI 1.45-5.06) in the overall cohort ($p<0.05$). Neck nodal metastases were associated with higher risk of recurrence in OBS cohort (HR 3.82, 95% CI 1.91-7.66; $p<0.05$) but not in the PD1 cohort. Rates of $\geq$ Grade 3 toxicities were 10.9% with PD1 and 20.0% with TT; discontinuation due to toxicity occurred in 25.0% and 30.0%, respectively. No new safety signals were observed. Rates of unresolved toxicity at last follow-up were 26.9% in PD1 and 7.7% in TT cohorts. **Conclusions:** In this large international study, adjuvant PD1 or TT did not significantly improve RFS or DMFS compared to OBS in pts with resected stage IIIA melanoma. Prognosis in stage IIIA melanoma is favourable and outcomes after adjuvant therapy in this population needs further study in prospective randomised trials. Research Sponsor: None.

Baseline pt characteristics and median follow-up.

	PD1, n=256	TT, n=65	OBS, n=292
Male, n (%)	150 (58.6)	31 (47.7)	151 (51.7)
Age, median (years) (IQR)	54 (42-64)	49 (37-58)	58 (46-68)
ECOG PS 0-1, n (%)	246 (96.1)	65 (100)	283 (97.0)
Breslow thickness, median (mm) (IQR)	1.3 (1.1-1.7)	1.3 (1.1-1.5)	1.3 (1.1-1.6)
Mitotic rate, median (per mm^2) (IQR)	3.0 (1.0-5.0)	2.0 (1.8-4.0)	2.0 (1.0-4.0)
Presence of ulceration, n (%)	22 (8.6)	2 (3.1)	8 (2.7)
Lymph node involvement, N1a, n (%)	206 (80.5)	55 (84.6)	253 (86.6)
Maximum diameter of the largest node, median (mm) (IQR)	1.2 (0.5-2.0)	1.0 (0.3-2.0)	0.5 (0.1-1.1)
Complete lymph node dissection, n (%)	55 (21.5)	4 (6.2)	24 (8.2)
BRAF^{V600} mutation, n (%)	91 (35.5)	65 (100)	90 (30.8)
Follow-up, median (years) (IQR)	2.7 (1.7-3.4)	2.4 (1.5-3.1)	2.6 (1.5-3.4)

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9519 **Poster Discussion Session**

Cemiplimab for kidney organ transplant recipients with advanced cutaneous squamous cell carcinoma: CONTRAC-1.

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Background: Solid organ transplant recipients are often excluded from immunotherapy trials given the risk of allograft rejection and loss. We report the results of the first prospective study using the PD-1 inhibitor Cemiplimab (Cemi) for kidney transplant recipients (KTR) with advanced, incurable cutaneous squamous cell carcinoma (cSCC), adopting a standardized approach to immunosuppression (IS) with mTOR inhibition and dynamic prednisone (NCT04339062). **Methods:** This single-arm, open-label prospective clinical trial enrolled KTRs (eGFR $\geq$30 mL/min without proteinuria) with advanced cSCC, ECOG $\leq$2, measurable disease (RECIST v1.1), with no prior immunotherapy exposure. KTRs received mTOR inhibition (target trough 4-6 ng/mL) with a prednisone taper each cycle (40 mg on day -1 to 3, 20 mg days 4-6, 10 mg days 7-20) along with Cemi 350 mg IV every 21-days. Primary endpoint: rate of rejection (futility defined as $\geq$2/3 or 4/6 KTRs with rejection events). Secondary endpoints: overall response rate (ORR), duration of response, progression-free survival (PFS), overall survival (OS), infection rates. Exploratory: baseline tumor PD-L1 score, molecular and immunologic predictors of response. **Results:** From 11/2020 to 1/2023, 10 KTRs (median years from transplant: 8, range: 3-31) enrolled including 8 (80%) men, median age 64 (range: 43-86), median eGFR 48 (range: 32-60) often with head and neck primaries (9, 90%) and distant metastases (7, 70%). Six (60%) had prior systemic therapy. For mTOR inhibition, 7 (70%) received sirolimus and 3 (30%) everolimus. At a median follow-up of 6.3 months (range: $<$ 1-24.9), no patients experienced kidney allograft rejection or loss. Of 8 evaluable patients, ORR was 50% (2 CR, 2 PRs), while 4 had PD. At data cutoff no responder had progressed, with 2/4 in response $>$ 18 months (range: $<$ 1-22.7+). One patient is pending first restaging; 1 was unevaluable (died before first restaging). One KTR with initial PD experienced a subsequent durable response to cetuximab. Fatigue (40%) and limb edema (30%) were the most common treatment-related adverse events (TRAEs). Grade 3+ TRAEs occurred in 5 (50%) patients including diarrhea, infections (n = 3), and electrolyte derangements; there were no Cemi-related deaths. Median PFS was 7.9 mos (95%CI: 1.2-not reached [NR]); the 3-month OS estimate was 61% (95%CI: 27-83). Baseline tumor PD-L1 scores ranged from 0-5%; median TMB was 49 muts/Mb (range: 10-97). Tumor mutations in *TP53, CDKN2A*, and *NOTCH1* were common. Exploratory tumor/circulating multiparametric immune profiling and circulating tumor (ct)DNA findings will be presented. **Conclusions:** Using IS with mTOR inhibition and dynamic prednisone resulted in no kidney allograft rejection among KTRs treated with Cemi for advanced cSCC. Durable anti-tumor efficacy was observed. mTOR inhibition with prednisone should be the preferred IS regimen when treating KTRs with anti-PD-1 therapy. Clinical trial information: NCT04339062. Research Sponsor: Regeneron Pharmaceuticals.

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9520 **Poster Discussion Session**

Role of nivolumab maintenance therapy in advanced melanoma patients following severe immune-related adverse events from combination nivolumab and ipilimumab.

Anna Maloney, Anita Giobbie-Hurder, Miklos C. Fogarasi, Patrick Alexander Ott, F. Stephen Hodi, Tamara A. Sussman, Ann W. Silk, Rizwan Haq, David Liu, Megan Leigh Insco, Elizabeth Iannotti Buchbinder; Frank H Netter MD School of Medicine, North Haven, CT; Dana-Farber Cancer Institute, Boston, MA; Quinnipiac University, Hamden, CT; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: The combination of ipilimumab (ipi), and nivolumab (nivo) has been shown to be a highly effective treatment for metastatic melanoma. However, immune-related adverse events (irAEs) are common with this treatment, leading to treatment interruption and the use of immunosuppressive agents. There are no data on the impact of resuming single agent nivo on survival outcomes following recovery from the irAE and completion of immunosuppressive treatment. Some physicians hold therapy permanently as done on clinical trials and other physicians resume nivo after steroid taper. **Methods:** In this retrospective analysis, we examined a cohort of patients treated with ipi/nivo who developed irAEs that required treatment interruption and immunosuppressive therapy. The differences in practice patterns among physicians at our institution allowed us to examine the effect of single agent nivo resumption on survival after treatment of irAEs. Multivariate analysis of clinical factors associated with improved survival was performed. **Results:** We identified 165 patients who were treated with ipi/nivo and developed irAEs requiring treatment interruption and immunosuppressive therapy. To remove any impact of immediate disease progression on the analysis patients who progressed on ipi/nivo prior to or during treatment hold were removed from analysis. Of the remaining 131 patients, 45 resumed single agent maintenance nivo following the resolution of toxicity and completion of steroid taper. When stratified by age and adjusted for sex, M-stage, LDH, duration of therapy, and type of irAE causing the treatment pause, the effect of resumption of nivo upon survival remained highly significant ($p = 0.001$). Patients who resumed nivo had an 82% reduction in the hazard of death compared with patients who had not yet or never resumed nivo (HR: 0.18, 95% CI: 0.06 to 0.52). Of the patients who resumed nivo, 12 (26%) patients had subsequent irAEs with 5 patients having grade 3 irAEs (only one of whom had a recurrence of the prior ipi/nivo associated toxicity) and no grade 4 or 5 irAEs were noted. **Conclusions:** The resumption of single agent maintenance nivolumab following a treatment hold for ipi/nivo associated irAE and completion of immunosuppressive therapy increased overall survival compared to discontinuing nivo permanently in patients with metastatic melanoma after stratification for many factors. Toxicity observed post resumption of single agent nivolumab was manageable with no severe irAEs observed. These results suggest that restarting maintenance nivo post irAEs should be studied prospectively. Research Sponsor: Dana-Farber Cancer Institute.

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9521 **Poster Session**

Real-world treatment patterns and clinical outcomes among subgroups of BRAF-positive metastatic melanoma patients treated with dabrafenib + trametinib.

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Background: Whether disease attributes such as tumor burden or central nervous system (CNS) metastases can affect outcomes for patients with BRAF+ metastatic melanoma (MM) is currently unclear. This study examined real-world patient characteristics, treatment patterns, and clinical outcomes among subgroups of patients with BRAF+ MM treated with dabrafenib + trametinib (dab/tram) in the United States. **Methods:** This retrospective cohort study used the nationwide Flatiron Health electronic health record-derived de-identified database from 1/1/2014 to 9/30/2021. Included patients were aged ≥18 years with a diagnosis of BRAF+ MM and received first-line (1L) dab/tram. Patients were stratified into 4 subgroups: high tumor burden (HTB; ≥3 sites of metastasis and lactate dehydrogenase [LDH] ≥333 IU/L), low tumor burden (LTB; <3 sites of metastasis and LDH <333 IU/L), with CNS metastases (prior to 1L dab/tram), and without CNS metastases (prior to 1L dab/tram). Patient characteristics and treatment patterns were evaluated descriptively. Given the potential patient overlap between subgroups, no comparative statistics were conducted. Real-world progression-free (rwPFS) and overall survival (OS) were explored from dab/tram initiation. **Results:** Among 460 included patients (mean age 60 years, 64% male), 66 (14%) had a HTB, 69 (15%) had a LTB, 164 (36%) had CNS metastases, and 296 (64%) did not. Patient characteristics were comparable across the subgroups. Over 60% of HTB patients had documented metastases in each of the liver, lung, bone, lymph nodes, and other sites. Only lung metastases had >60% prevalence among patients with a LTB. Overall, 51% of the included patients went on to receive a second-line therapy; LTB patients and those without CNS metastases had a longer time to next therapy. The median rwPFS and OS were significantly shorter among patients with a HTB vs LTB, and among patients with vs without CNS metastases (Table). **Conclusions:** Both tumor burden and presence of CNS metastases appear to have a significant impact on survival among BRAF+ MM patients treated with 1L dab/tram. With growing use of 1L immunotherapy in MM, 1L BRAF/MEK inhibitors are increasingly being used in patients with a worse prognosis, which may explain the lower rwPFS and OS with dab/tram when compared with clinical trials. Research Sponsor: Novartis Pharmaceuticals Corporation.

	Overall (N=460)	HTB (n=66)	LTB (n=69)	CNS metastases (n=164)	No CNS metastases (n=296)
Patients advancing to 2L therapy, n (%)	234 (51%)	33 (50%)	43 (62%)	75 (46%)	159 (54%)
Median time to 2L therapy, days (IQR)	179 (106-335)	140 (100-334)	169 (118-373)	163 (96-307)	181 (108-356)
Median rwPFS, months (95% CI)	5.5 (4.9-6.3)	4.2 (3.3-4.6)	8.4 (5.3-12.4)	3.9 (3.4-4.5)	7.4 (6.3-8.7)
Median OS, months (95% CI)	12.5 (10.5-14.7)	6.1 (4.8-12.9)	15.3 (12.0-21.7)	8.0 (6.0-9.2)	15.3 (12.5-19.0)

2L: second line; CI: confidence interval; IQR: interquartile range.

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9522 **Poster Session**

Subsets of interferon signaling and response to immune checkpoint blockade.

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Background: Interferon (IFN) signaling in tumors is critical for both response and resistance to immune checkpoint inhibitors (ICI). While PD-L1 is an approved biomarker for ICI response in some cancers, most have no approved biomarkers for ICI response. Further, there are no clinical strategies to predict IFN sensitive vs resistant states. We hypothesized that distinct patterns of IFN signaling in melanoma, including STAT1 (precursor to IFN signaling), phosphorylated STAT1 (pSTAT1, marker of active IFN signaling), and PD-L1 (canonical inhibitory output), are associated with response or resistance to ICI. **Methods:** Samples from 2 tissue microarrays of 97 patients total with metastatic melanoma who received ICI from 2011-2017 were randomized into discovery [D] or validation [V] cohorts. Multiplexed immunofluorescent microscopy was used to assess STAT1, pSTAT1, and PD-L1. 54 tumors were assessed for CD3. Signals were quantified via AQUA (Automated Quantitative Analysis). High vs low signals were defined around the discovery cohort median AQUA scores. Treatment response was assessed using RECIST, and 3-year survival was analyzed. For *in vitro* studies, 4 human melanoma cell lines were stimulated with IFNγ/β, and Western blots were performed for STAT1, pSTAT1, and PD-L1. **Results:** Median follow up time was 20.2 mos (range 0.9-95.4 mos). Higher overall histospot, tumor, and nuclear STAT1 were in responders (CR/PR/SD $>$ 6 mos) compared to non-responders (SD $<$ 6 mos/PD, histospot p = 0.029 [D] and 0.040 [V]) and were associated with improved survival (histospot HR 0.25 [95% CI 0.08-0.76] p = 0.015 [D]; HR 0.32 [95% CI 0.12-0.84] p = 0.021 [V]). PD-L1 and pSTAT1 did not validate as associated with ICI response/survival. While many tumors had concordant high/low STAT1, pSTAT1, and PD-L1, many also had a discordant STAT1 or PD-L1 predominance. To assess the basis of this discordance, we performed IFN stimulation and Western blots of melanoma cell lines. IFNβ upregulated STAT1 greater than PD-L1 in both acute and chronic settings ($p < 0.001$ and < 0.001), while chronic IFNγ upregulated PD-L1 compared to the acute setting (p = 0.039) but not STAT1 (p = 0.105). Therefore, we hypothesized patients with discordant STAT1 and PD-L1 expression may have differential responses to ICI. In the overall cohort, $STAT1^{high}PD\text{-}L1^{high}$ tumors (IFN engaged) were associated with improved survival compared to $STAT1^{low}PD\text{-}L1^{low}$ tumors (IFN low, HR 0.28 [95% CI 0.11-0.70] p = 0.007). Interestingly, $STAT1^{high}PD\text{-}L1^{low}$ tumors were associated with improved survival compared to $STAT1^{low}PD\text{-}L1^{high}$ tumors (HR 0.28 [95% CI 0.08-0.94] p = 0.04). Accordingly, $STAT1^{high}PD\text{-}L1^{high}$ and $STAT1^{high}PD\text{-}L1^{low}$ tumors had greater CD3 AQUA scores compared to $STAT1^{low}PD\text{-}L1^{low}$ tumors ($p < 0.001$ and p = 0.018 respectively). **Conclusions:** Combined STAT1 and PD-L1 expression patterns may better predict melanoma response to ICI and provide insight into IFN sensitive versus resistant states. Research Sponsor: U.S. National Institutes of Health; Melanoma Research Alliance / Bristol Meyers-Squibb Young Investigator Award.

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9523 **Poster Session**

The validity of a machine learning algorithm in predicting response to immune checkpoint inhibitors in melanoma.

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Background: We previously reported the development of a machine learning algorithm to predict immunotherapy response in patients with advanced melanoma using retrospectively collected pre-treatment histologic slides (Johannet et al, CCR 2021). In this study, we tested the validity of the same algorithm in two independent cohorts of melanoma patients enrolled in phase III clinical trials of immune checkpoint inhibitors (ICI), one metastatic, and one adjuvant. **Methods:** We examined 336 patients enrolled in CheckMate 067(NCT01844505) and CheckMate 238 (NCT02388906). We used deep convolutional neural networks (DCNN) to automatically segment images into three regions of interest: tumor, lymphocytes, and stroma. The algorithm was previously trained and tested to predict the complete and partial response (CR/PR) versus progression of disease (POD) and to predict the probability of progression-free survival (PFS) while on ICI. We tested the performance in the two cohorts; the first (CheckMate 067) included 164 patients with stage III/IV unresectable melanoma who received ipilimumab (n= 49), nivolumab (n = 59), or combination (n= 56) therapy as a first line, then tested whether the algorithm could perform as well in the second cohort (CheckMate 238) which included 172 patients with stage III/IV resectable melanoma who received adjuvant ipilimumab (n = 87) or nivolumab (n = 85) therapy as first line. **Results:** The segmentation classifier identified tumor within slides with an area under the curve (AUC) of 0.99. A combined model of DCCN and treatment predicted POD with an AUC of 0.72 in metastatic melanoma patients enrolled in Checkmate 067. The DCCN classified patients into high and low risk based on their likelihood of PFS ($P < 0.0001$). However, the same algorithm is not effective in predicting recurrence in patients treated in the adjuvant setting in Checkmate 238 (AUC 0.52). Retraining and testing using only patients treated in the adjuvant setting improved the AUC average to 0.65-0.70. **Conclusions:** Our results show the reproducibility of our previously developed algorithm in predicting response in patients with advanced metastatic melanoma. The inability of the model to predict recurrence in patients treated in the adjuvant setting might reflect the difference in the endpoint tested (response versus recurrence), which requires further training on larger datasets for this particular endpoint prediction, and/or the limited tumor volume in resected disease below a threshold that machine learning can predict a difference. Research Sponsor: U.S. National Institutes of Health.

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9524 **Poster Session**

Identification of RPTOR mutation as a novel predictor of efficacious immunotherapy in melanoma.

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Background: mTOR pathway is known to influence cancer immunity by metabolism reprogramming. RPTOR (Regulatory Associated Protein of MTOR Complex 1), one of mTOR pathway genes, which is involving in control of mammalian target of mTORC1 activity for regulating cell growth and survival. Whether mutations of RPTOR are associated with clinical efficacy of immune checkpoint inhibitors (ICIs) in melanoma is still ambiguous. **Methods:** In discovery cohort, we retrospective analyzed the genomic data of 418 melanoma samples which derived from seven immunotherapy studies (http://www.cbioportal.org/) to evaluate the relationship between RPTOR mutation status and efficacy of immunotherapy. Then in validation cohort, the predictive value of RPTOR mutation was confirmed in 320 melanomas from MSKCC cohort (http://www.cbioportal.org/). TMB was calculated as the total count of nonsynonymous mutations in coding sequence. We used the CIBERSORT to evaluate the 22 types immune cell infiltration status in TCGA melanoma cohort. **Results:** The TMB level of RPTOR-mutant patients was higher than RPTOR-wildtype patients in both discovery (Median [IQR]: 43.11 [23.76-140.15] vs. 6.13[2.07-13.66], $P < 0.001$) and validation (Median [IQR]: 37.38[20.17-84.95] vs. 8.85[3.35-21.07], $P < 0.001$) cohort. In discovery cohort, compared to RPTOR-wildtype patients, the RPTOR-mutant patients achieved prolonged OS (median OS: not reach, NR vs 22.7 months, HR (95%CI): 0.47(0.22-0.99), $P = 0.043$). This result was confirmed in validation cohort (median OS: NR vs. 42; HR (95%CI): 0.34 (0.11-1.0); $P = 0.049$). According to analysis of immune cell infiltration status, the mechanism of the predictive values of RPTOR mutations to ICI efficacy may be activated CD4 memory T cell more abundant in RPTOR-mutant tumors. **Conclusions:** RPTOR mutation is associated with higher TMB in ICI-treated melanoma patients. Survival analysis shows RPTOR mutation have a good link with longer OS after immunotherapy. These findings indicate that RPTOR mutation may serve as a potential predictive biomarker for ICIs in melanoma. Research Sponsor: None.

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9525 **Poster Session**

CHARLI: A phase Ib/II trial of ipilimumab-nivolumab-denosumab or nivolumab-denosumab in patients with unresectable stage III and IV melanoma.

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Background: Denosumab (deno) is an antibody directed against Receptor Activator of NF Kappa-b ligand (RANKL) with established indications as a bone anti-resorptive agent in several cancers. Preclinical studies and several case series suggest anti-RANKL can enhance the anti-tumor effect of immune checkpoint inhibitors possibly via modulation of Treg and M2 macrophages. We did a multicentre phase Ib/II trial (NCT03161756) to investigate the safety and efficacy of deno in combination with nivolumab (nivo) or ipilimumab-nivolumab (ipi-nivo). **Methods:** Patients (pts) with unresectable stage III or IV melanoma were recruited to either Arm A (nivo-deno) or Arm B (ipi-nivo-deno) as first-line therapy. In Arm A pts received nivo 3 mg/kg IV q2 weekly for 4 doses and deno 120 mg SC on D1, D8, D15, D29 and then maintenance nivo 480 mg IV with deno 120 mg SC q 4 weekly. In Arm B pts received combined ipi 3mg/kg with nivo 1 mg/kg IV 3 weekly for 4 doses with deno 120 mg SC on D1, D8, D15, D29 followed by 4 weekly maintenance nivo 480 mg with deno 120 mg. Co-primary endpoints were median PFS and grade 3-4 treatment related adverse events (TRAE) of interest. Secondary endpoints were objective response rate (ORR) and overall survival (OS). **Results:** 27 pts (15 males, median age 67 years, 48% (13/27) stage IVM1c, 26% elevated LDH, 31% $BRAF^{V600}$ mutant) were enrolled in Arm A and 24 of 25 evaluable pts (16 males, median age 62, 46% (11/24) stage IVM1c, 13% (3/24) stage IVM1d, 30% elevated LDH and 33% $BRAF^{V600}$ mutant) were enrolled in Arm B. Median follow up was 30.8 months (m) for Arm A and 24.8 m for Arm B. The RECIST 1.1 ORR was 56% (n=15/27, 15% [4/27] complete responses [CR] and 41% [11/27] partial response [PR]) for Arm A and 71% (17/24, 25% [6/24) CR and 46% [11/24] PR) for Arm B. The median PFS in both arms has not been reached with 12 month PFS rates of 59% (95%CI: 43-81) and 63% (95%CI: 46-88) for Arms A & B, respectively. Grade 3-4 TRAE were 11% (3/27) in Arm A and 71% (17/24) in Arm B. Common TRAE (≥10%) in Arm A was rash (52%), pruritus (30%), fatigue (26%), nausea (19%), diarrhoea/colitis (15%), arthralgia (11%), vitiligo (11%), hyperthyroidism (11%). Common TRAE (≥10%) in Arm B included rash (63%), fatigue (54%), diarrhoea/colitis (54%), hepatitis (46%), hyperthyroidism (29%), pneumonitis (29%), pruritus (25%), increased GGT (17%), hypothyroidism (17%), hypocalcaemia (13%). Arm B G3-4 TRAE included diarrhoea/colitis (25%), pneumonitis (17%) and hepatitis (13%). **Conclusions:** Nivo-deno and ipi-nivo-deno had numerically similar G3-4 TRAE compared to nivo and ipi-nivo. The median PFS, 12 month PFS and ORR for nivo-deno and ipi-nivo-deno are encouraging compared with CHECKMATE 067. Clinical trial information: NCT03161756. Research Sponsor: Amgen and Bristol Myers Squibb.

	Arm A (n=27)	Arm B (n=24)
Median age (yr)	67	62
Stage IVM1C %	48	46
Stage IVM1D %	NA	13
High LDH %	26	30
ORR n (%)	15 (56)	17 (71)
CR n (%)	4 (15)	6 (25)
PR n (%)	11 (41)	11 (46)
SD n (%)	4 (15)	1 (4)
mPFS	Not reached	Not reached
PFS 12 m %	59	63

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9526 **Poster Session**

Leveraging longitudinal clinical annotations and panel sequencing to characterize dynamics of organotropism in metastatic melanoma.

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Background: Although metastasis plays a major role in the mortality and morbidity of melanoma, patterns of metastasis and drivers of organotropism have not been well characterized clinically. Although previous efforts have been made to examine genomic drivers of organotropism, a longitudinal examination of metastasis dynamics has not been well characterized clinically. **Methods:** To address these questions, we leveraged a clinico-genomic dataset of patients with metastatic melanoma (Kehl et al. 2021). From this dataset, we assembled a cohort consisting of 26,143 artificial intelligence-annotated imaging reports from 879 patients with metastatic melanoma with an average of 2 years of followup after initial metastatic diagnosis. Annotated metastasis sites included brain, bone, adrenal, liver, lymph node, lung, and mesentery. All patients were evaluated at the Dana-Farber Cancer Institute, and each patient has at least one tumor biopsy sequenced with OncoPanel, a next-generation sequencing panel that identifies mutations in 447 cancer-related genes. Lifetime incidence of metastatic sites was defined as whether a patient ever had a report annotated with that site. Time-to-event analyses on metastatic sites used the acquisition of a metastatic site as the event of interest. For each patient index dates were defined as the date of the first scan with cancer present. We used cumulative incidence models to examine the incidence of each site in our cohort, and both cause-specific hazard models and Fine-Gray modeling to account for competing events and determine the effect of genomic covariates. **Results:** For lifetime metastasis status, the overall incidence varied by site, with LN being the most common, occurring in ~75% of patients, and mesentery the rarest, occurring in ~12% of patients. For lifetime metastasis status, patients with adrenal metastases were positively enriched for mutations in SETD2 ($P < 0.005$). Among the significant genes for all sites were many genes encoding epigenetic modifiers. In the time-to-event setting, the order of the cumulative incidence functions for each site matched the lifetime frequency of sites. Through time-to-event analysis we found genes whose mutant status were significantly associated with a change in risk and/or rate of certain metastatic sites. Among other results, we found that having a mutation in SETD2 is significantly positively associated with an increase rate and risk of adrenal metastases (cause-specific HR 2.4, $P < 0.005$, Fine-Gray HR 2.6, $P < 0.005$), and NRAS mutations were significantly associated with lower rate and risk of liver metastasis (cause-specific HR 0.59 $P < 0.05$, Fine-Gray HR 0.58 $P < 0.01$). **Conclusions:** By using time-to-event analysis with longitudinal metastatic annotations, we identify potential drivers of organotropism in melanoma patients. Research Sponsor: U.S. National Institutes of Health.

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9527 **Poster Session**

Preliminary safety and efficacy results from an open-label, multicenter, phase 1 study of RP2 as a single agent and in combination with nivolumab in a cohort of patients with uveal melanoma.

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Background: Uveal melanoma, although rare, represents the most common primary intraocular tumor in adults and is associated with high risk of liver metastases. Effective treatments are limited as uveal melanoma is an immunologically cold tumor that does not respond well to immunotherapy. RP2 is an enhanced-potency oncolytic herpes simplex virus type 1 expressing human granulocyte-macrophage colony-stimulating factor, fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R−), and an anti–CTLA-4 antibody-like molecule. Here, we present updated safety and efficacy data of RP2 monotherapy and RP2 + nivolumab (nivo; anti–PD-1) in patients (pts) with uveal melanoma. **Methods:** Pts ≥18 years old with histologically or cytologically confirmed advanced or metastatic non-neurological solid tumors (including uveal melanoma) who progressed on or could not tolerate standard therapy were included; pts had ≥1 measurable and injectable tumor (≥1 cm). After determination of the recommended phase 2 dose of RP2 (concentration of 10^6 plaque-forming units [PFU]/mL intratumorally [IT] once followed by up to 7 additional IT doses at 10^7 PFU/mL; [≤10 mL total/treatment day with amount per lesion determined by tumor diameter]), pts received RP2 monotherapy every two weeks (Q2W) or RP2 Q2W + nivo (NCT04336241). Responses were assessed using modified Response Evaluation Criteria in Solid Tumors version 1.1. **Results:** As of December 30, 2022, 17 pts with uveal melanoma were enrolled (RP2 monotherapy, n = 3; RP2 + nivo, n = 14). The majority of pts received both anti–PD-1 and anti–CTLA-4 therapy (12/17, 70.6%) and 17.6% received ≥3 prior lines of therapy. The overall objective response rate for the 14 pts with sufficient follow up for analysis was 28.6% [4/14] (all partial responses [PRs]; RP2 monotherapy, 1/3; RP2 + nivo, 3/11). The disease control rate (complete response + PR + stable disease [SD]) was 57.1% (8/14; 4 pts with SD in RP2 + nivo cohort). The median (range) duration of response at the data cut-off was 5.8 (1.7–14.7) months. The most common overall Grade 1–2 treatment-related adverse events (TRAEs; ≥20%) were pyrexia, chills, fatigue, and hypotension. The only Grade 3 TRAE occurring in > 1 pt was hypotension (2 pts receiving RP2 + nivo); no Grade 4–5 TRAEs were observed. **Conclusions:** Preliminary RP2 monotherapy and RP2 + nivo data demonstrated a favorable safety profile and meaningful antitumor activity in pts with metastatic uveal melanoma, an immunologically cold tumor with few effective treatment options. These data continue to support the hypothesis that IT oncolytic immunotherapy expressing anti–CTLA-4 in combination with anti–PD-1 may provide clinically meaningful benefit in pts with hard-to-treat/unresponsive tumors. Clinical trial information: NCT04336241. Research Sponsor: Replimune Inc.

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Anti-PD1 plus BRAF/MEK inhibitors (triplet therapy) after failure of standard therapy in patients (pts) with advanced melanoma.

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Background: Preclinical models support the combination of immune checkpoint inhibitors (ICI) with targeted therapy (TT), suggesting a synergistic effect; however, clinical trials evaluating the efficacy of triplet combination in first-line setting showed limited advantage compared to TT only. Early data from the phase II TRIDeNT (NCT02910700) study showed promising clinical activity in anti-PD1 refractory pts. We sought to evaluate the efficacy of combined TT plus anti-PD1 after the failure of standard therapy in pts with advanced melanoma. **Methods:** This retrospective, multicenter study included pts with advanced melanoma who were treated with a BRAF inhibitor and a MEK inhibitor in combination with a PD1 inhibitor after failure of a minimum of one standard therapy in seven major melanoma centers between February 2016 and July 2022. Demographics, disease characteristics, therapy details, and outcome data were evaluated. **Results:** 59 pts were identified; med age was 48 yrs (range, 24-80), 32 pts (54.2%) were males, 20 pts (33.9%) had ECOG PS 1, 46 pts (78%) had 3 or more metastatic sites, 40 pts (67.8%) had brain metastases, and 25 (42.2%) had LDH levels above the upper limit of normal before initiation of triple therapy. Median follow-up time was 16.2 months (IQR, 6.02-20.81). Median number of previous treatment lines was 2 (range, 1-6); 40 pts (67.8%) were pretreated with at least one line of ICI and TT in any sequence. Of 55 pts who received ICI (n = 41 CTLA4 plus PD1; n = 9 PD1 mono; n = 2 CTLA4 mono; n = 3 PD1-based therapy) prior to triplet therapy, 44 pts (80%) were primary resistant (progressive disease (PD); stable disease (SD) for $<$ 6 months), and 11 pts (20%) secondary resistant (complete response (CR), partial response (PR), SD for $>$ 6 months) to the ICI therapy. Treatment with triplet therapy resulted in an overall response rate (ORR) of 44.1% (n = 26) and a disease control rate (DCR) of 55.9% (n = 33) with a median duration of response of 13.7 months (range, 5.4-33.2). Median PFS for the entire cohort was 6 months (95% CI, 3.88-8.08), with a 12-month PFS of 29.4% (95% CI, 17.8-42.1) and a 24-month PFS of 20.2% (95% CI, 11.0-32.8). Median OS was 15.7 months (95% CI, 8.1-23.3 months), with a 12-month OS of 52.7% (95% CI, 39.1-65.7) and a 24-month OS of 43.2% (95% CI, 29.6-55.9). Pts with extracerebral PD prior to triplet therapy (40.7%, n = 24) showed an ORR of 50%, pts with intracerebral PD (32.2%, n = 19) of 47.4%, and pts with global PD (27.1%, N = 16) of 31.3%. Treatment-related adverse events (TRAE) of grade $\geq$3 occurred in 17 of 59 pts (28.8%), of which cytokine release syndrome (n = 7) and hepatitis (n = 3) were the most common. In 16.9% (n = 10) of pts, TRAEs led to treatment discontinuation. **Conclusions:** Triple therapy has shown promising efficacy in heavily pretreated pts with advanced melanoma and may represent a treatment option after failure of standard therapy with ICI and TT. Research Sponsor: None.

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9529 **Poster Session**

Risk of further progression or death among durable progression-free survivors with melanoma in PD-1 blockade trials: Implications for imaging surveillance.

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Background: Durable progression-free survivors (dPFSors) over 2 years have been reported among melanoma patients treated with PD-1 blockade. However, non-negligible risk of further progression still exists and the optimal imaging surveillance interval is unknown. **Methods:** Individual patient data of progression-free survival (PFS) were extracted from PD-1 blockade clinical trials with follow-up of at least 5 years of PFS events. Co-treatment with anti-CTLA4 antibody was allowed. Patients with PFS of at least 2 years were considered as dPFSors. Conditional risk of progression or death with 95% CI was estimated based on a piece-wise exponential survival model, with the assumption that within each year from the beginning of the third year, the risk of progression/death (P/D) was constant. Conditional risks of P/D every 3, 4, 6, and 12 months in each subsequent year were calculated with 95% confidence interval (CI). We pre-specified three maximal risk levels – 10%, 15%, and 20% at each imaging scanning interval. An interval is considered as acceptable if the 95% CI upper bound of the risk at each scan is lower than a pre-specified risk level. **Results:** Of 1495 melanoma patients from 3 clinical trials, 474 (31.7%) were dPFSors. Among them, the PFS probability for additional 3 years was 76.4%. During the 3 years, no more than 5.0% of patients had P/D in any quarters. The yearly risk of P/D was 15.5% (95% CI 13.7% - 17.3%), 8.8% (6.8% - 10.8%), and 6.3% (3.8% - 8.8%) during the 3rd, 4th, and 5th year, respectively. Under risk at 10%, 15%, and 20%, melanoma dPFSors can be scanned every 6, 6, and 12 months during the 3rd year, every 6, 12, and 12 months during the 4th, and every 12, 12, and 12 months during the 5th, respectively. **Conclusions:** Based on their own risk tolerance level, our findings allow clinicians and dPFSors make data-driven decisions regarding imaging surveillance schedule beyond every 3 months. Research Sponsor: U.S. National Institutes of Health.

Proposed imaging surveillance intervals according to three risk tolerance level per scan.

	10%	15%	20%
3rd year	Every 6 months (Risk: 8.1%, 95% CI 7.2% - 8.9%)	Every 6 months (Risk: 8.1%, 95% CI 7.2% - 8.9%)	Every 12 months (Risk: 15.5%, 95% CI 13.7% - 17.3%)
4th year	Every 6 months (Risk: 4.5%, 95% CI 3.6% - 5.5%)	Every 12 months (Risk: 8.8%, 95% CI 6.8% - 10.8%)	Every 12 months (Risk: 8.8%, 95% CI 6.8% - 10.8%)
5th year	Every 12 months (Risk: 6.3%, 95% CI 3.8% - 8.8%)	Every 12 months (Risk: 6.3%, 95% CI 3.8% - 8.8%)	Every 12 months (Risk: 6.3%, 95% CI 3.8% - 8.8%)

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9530 **Poster Session**

Early safety and efficacy from a phase I clinical study of TWP-101, a novel CD137 agonist antibody, in patients with advanced melanoma and urothelial carcinoma.

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Background: CD137 plays the roles as a potent co-stimulator of both adaptive and innate immune cells, being an attractive target for cancer immunotherapy. TWP-101 is a fully humanized agonistic anti-CD137 monoclonal IgG4 antibody, targeting a novel epitope of CD137 with a unique mechanism of actions as a CD137 agonist but not CD137 ligand antagonist. The phase I study of TWP-101 in patient (pt)s with advanced melanoma and urothelial carcinoma was initiated (NCT04871334). **Methods:** Enrolled pts were advanced melanoma refractory to standard therapy. Dose-escalation includes accelerated titration (0.01 and 0.03mg/kg) and conventional Fibonacci 3+3 dose levels (0.1, 0.3, 1.0 and 3.0 mg/kg). TWP-101 was administered intravenously every Q2W until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. The primary objectives were to define the safety profile, to determine the maximum tolerated dose and RP2D of TWP-101. Secondary objectives were to evaluate pharmacokinetics (PK), immunogenicity and preliminary clinical efficacy. Exploratory objectives were to determine pharmacodynamics (PD) biomarkers. **Results:** From Feb 2021 to Mar 2022,13 melanoma pts (median age 54 years, range 39-73; 6 men, 7 women; median 2 prior lines of therapy, range 1-6; 12 with prior immunotherapy) were treated. The following five dose levels had been evaluated from 0.01 to 1.0 mg/kg. 3mg/kg dose escalation is ongoing, no MTD has been reached. The median treatment time was 16 wks. (range 2-59). On cutoff date of October 31, 2022, 13 pts discontinued treatment due to progression disease (n = 12) and protocol deviation (n = 1). No DLTs were observed. 9 pts (69.2%) experienced treatment-related adverse events (TRAE). The most common TRAEs (≥10%) were neutropenia (23.1%), leukopenia (15.4%), hypertriglyceridemia (15.4%), anemia (15.4%), hyponatremia (15.4%). 1 pt experienced grade 3-4 TRAEs: hyponatremia, Asthenia and reduced appetite. In all TRAEs, one grade 1 decreased free triiodothyronine and one grade 2 pyrexia were possibly related, and all other TRAEs, including 2 treatment-related SAEs (1 grade 4 hyponatremia and 1 grade 2 subarachnoid hemorrhage), were identified as possibly unrelated. Deaths were due to progression disease (n = 3). Preliminary PK analysis showed dose-proportional kinetics. For 12 evaluable pts, 2 pts achieved PR (16.7%), 5 pts was SD. DCR was 58.3%. Median PFS was 16 wks. (range 16-60), PFS of 2 PR pts was 24 and 60 wks. **Conclusions:** TWP-101 demonstrated a good safety profile without hepatotoxicity frequently observed with other studied CD137 antibodies. Both favorable tolerability and preliminary antitumor activity warrant further evaluation in pts with advanced melanoma and urothelial carcinoma. Clinical trial information: NCT04871334. Research Sponsor: herawisdom Biopharma Co. Ltd.

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Encorafenib (enco) + binimetinib (bini) + pembrolizumab (pembro) for unresectable locally advanced or metastatic BRAF V600-mutant melanoma: Results from STARBOARD safety lead-in (SLI).

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Background: BRAF inhibitors (BRAFi) + MEK inhibitors (MEKi) (eg, enco + bini) and immune checkpoint inhibitors (CPIs) (eg, pembro) are approved for patients (pts) with BRAF V600-mutant metastatic melanoma. Combinations of BRAFi + MEKi with CPIs further improve outcomes and may offer additional treatment strategies. STARBOARD (NCT04657991) is an ongoing randomized, double-blinded, placebo-controlled, phase 3 study of enco + bini + pembro vs pembro in pts with unresectable locally advanced or metastatic BRAF V600-mutant cutaneous melanoma. Here we present the SLI results. **Methods:** Key inclusion criteria were histologically confirmed unresectable/metastatic BRAF V600E/K-mutant cutaneous melanoma and $\leq$1 prior systemic therapy for unresectable/metastatic disease. Pts received enco 450 mg QD + bini 45 mg BID + pembro 200 mg IV Q3W (COMBO450+P) or enco 300 mg QD + bini 45 mg BID + pembro 200 mg IV Q3W (COMBO300+P). The primary objective was to identify the recommended phase 3 dose (RP3D). The primary endpoint was dose-limiting toxicity (DLT) incidence; secondary endpoints included safety, objective response rate (ORR), time to response (TTR), and PFS (post hoc). **Results:** 20 pts received COMBO450+P and 17 COMBO300+P (cutoff: Dec 2, 2022). See table for baseline characteristics. 1 pt had a DLT with COMBO450+P: Grade (G) 3 drug-induced liver injury with concurrent G4 ALT increase and G3 bilirubin increase that resolved. 2 pts had DLTs with COMBO300+P: 1 with G3 rheumatoid arthritis flare and 1 with inability to receive drug due to G4 arthralgia, G4 back pain, G4 pyrexia, G3 chills, G3 headache, G3 paranesthesia, and G3 maculopapular rash. Drug-related AEs led to permanent discontinuation in 4, 5, and 6 pts for enco, bini, and pembro, respectively. 1 pt in the COMBO300+P arm died $<$28 days after discontinuing all study treatments due to disease progression. See table for antitumor activity data. **Conclusions:** Safety across cohorts was comparable and consistent with the known safety profile of each agent. Both regimens were generally tolerable; COMBO450+P was chosen as the RP3D based on the totality of the safety data. The phase 3 portion of STARBOARD is ongoing. Clinical trial information: NCT04657991. Research Sponsor: Pfizer Inc.

Baseline characteristics and antitumor activity.

	COMBO450+P	COMBO300+P
Baseline characteristics	**n=20**	**n=17**
Median age, y	51.5	54.0
ECOG PS 0, n (%)	15 (75.0)	15 (88.2)
BRAF V600E (local test), n (%)	18 (90.0)	14 (82.4)
Prior adjuvant BRAFi/MEKi, n (%)	2 (10.0)	0
Prior adjuvant CPI, n (%)	2 (10.0)	0
Median FU, months	**9.7**	**10.9**
Antitumor activity	**n=19**	**n=16**
ORR, n (%)	12 (63.2)	8 (50.0)
[95% CI]	[41.0, 80.9]	[28.0, 72.0]
CR	1 (5.3)	1 (6.3)
PR	11 (57.9)	7 (43.8)
SD	4 (21.1)	3 (18.8)
PD	0	1 (6.3)
Not evaluable	3 (15.8)	4 (25.0)
Response duration ≥6 mo, n (%)	6 (50)	6 (75)
Median TTR, wk	9.0	9.2
Median PFS, mo (95% CI)	9.2 (7.1, NE)	NE (4.8, NE)
Pts at risk, n	20	17
Pts with event, n (%)	7 (35)	6 (35.3)

NE, not estimable.

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9532 **Poster Session**

A prediction model for response to immune checkpoint inhibition in advanced melanoma.

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Background: Immune checkpoint inhibition (ICI) has greatly improved the prognosis for advanced melanoma in the last decade. However, it is still difficult to predict who will benefit from treatment. We aimed to develop a multivariable prediction model for response to ICI, using clinical data including primary melanoma characteristics. **Methods:** We used a population-based cohort of 3525 patients with advanced cutaneous melanoma treated with anti-PD-1-based therapy, originating from the Dutch Melanoma Treatment Registry. The endpoint of the study was objective response to ICI within 6 months after treatment initiation. The model considered 15 candidate predictor variables, was developed with logistic regression using Akaike information criterion-informed backward selection, and was internally validated with bootstrap resampling. Performance evaluation included calibration and discrimination. We used multiple imputation to account for missing data. **Results:** Patients received anti-PD-1 monotherapy (n = 2366) or ipilimumab plus nivolumab (n = 1159) in any treatment line. Median follow-up time was 15 months and 1311 patients (39%) had an objective response within 6 months. The prediction model for response included sex, serum lactate dehydrogenase, World Health Organization performance score, type of systemic therapy, line of systemic therapy, stage of disease, location of primary melanoma, type of primary melanoma, satellites and/or in transit metastases at time of primary diagnosis, and time to first distant recurrence. The model was well-calibrated. The AUC was 0.664 (95% confidence interval [CI] 0.645-0.682), and the over-optimism adjusted AUC was 0.649 (95% CI 0.631-0.667). The range of predicted response probabilities was 6-78%. Based on these probabilities, patients were categorized into quartiles. The median predicted response probability was 25% (interquartile range [IQR] 21-28%) for the lowest quartile and 54% (IQR 50-59%) for the highest quartile. Compared to the lowest response quartile, patients in the highest quartile had a significant longer median PFS (19.9 versus 2.8 months; $p < 0.001$) and median OS (66.5 versus 8.4 months; $p < 0.001$). **Conclusions:** We present a model based on both clinical variables and primary melanoma characteristics capable of predicting response to ICI in patients with advanced melanoma. This model can discriminate between patients with a very good and very poor prognosis. Research Sponsor: None.

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9533 **Poster Session**

A phase I, randomized, controlled, multicentre trial of isolated hepatic perfusion in combination with ipilimumab and nivolumab in patients with uveal melanoma metastases (the SCANDIUM 2 trial).

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Background: Uveal melanoma is a rare disease characterized by liver metastasis and a very poor prognosis. In patients with metastatic UM, a single treatment with isolated hepatic perfusion (IHP) with high dose melphalan has shown response rates of 40%, while immune checkpoint blockade with ipilimumab (3 mg/kg) in combination with nivolumab (1 mg/kg) every third week (IPI3/NIVO1 q3w) for four cycles followed by nivolumab monotherapy has shown response rates of 11-18%. The impact of these treatments on overall survival, especially if combined, is unclear. This phase I trial investigates the safety and tolerability of the combination of IHP and IPI3/NIVO1. **Methods:** Eligible in this multicenter open, randomized, controlled, phase I trial, were patients with liver dominant metastatic uveal melanoma who had not received previous systemic treatment. Patients were randomized to receive either (Arm A) IHP followed by combination immunotherapy (four cycles IPI3/NIVO1 q3w) or (Arm B) one neoadjuvant cycle of IPI3/NIVO1 prior to IHP followed by three cycles IPI3/NIVO1 q3w. Thereafter, both Arm A and B received monotherapy with nivolumab (480 mg q4w) for up to 1 year. IHP was performed using melphalan 1mg/kg perfused through the liver for 60 minutes under hyperthermia (40°C). The primary endpoint was incidence and severity of adverse events while, secondary endpoints included response according to RECIST v1.1 criteria reported according by the local investigator. **Results:** A total of 18 patients were included and randomized, nine to Arm A and nine to Arm B. Three patients did not undergo IHP as planned, one due to perioperative complications (Arm A), one due to extensive metastatic liver infiltration ($>$ 50% liver volume) (Arm B) and one due to encephalitis related to neoadjuvant IPI3/NIVO1 (Arm B). A total of 20 serious adverse events (SAEs) were reported in eleven patients. There were ten SAEs in each arm, with no treatment related deaths. In total, 11 of 18 patients (six in Arm A and five in arm B) did not complete the planned four cycles of IPI3/NIVO1, with a mean of 2.4 cycles in Arm A and 3.0 cycles in Arm B. Response was evaluable in 17 patients, with the best clinical responses reported as three complete responses (18%), four partial responses (24%), seven stable disease (41%) and three progressive disease (18%). The overall response rate was 63% in Arm A (5/8) and 22% in Arm B (2/9). **Conclusions:** For previously untreated patients with liver dominant metastatic uveal melanoma, treatment with IHP in combination with IPI3/NIVO1 had a high, yet manageable toxicity profile. The efficacy of this combination treatment is encouraging, however, one cycle of neoadjuvant IPI3/NIVO1 given before IHP did not seem beneficial, neither in regards to safety nor efficacy. Clinical trial information: NCT04463368. Research Sponsor: The Assar Gabrielsson Foundation, American Association for Cancer Research, Bristol-Myers Squibb, Knut and Alice Wallenberg Foundation, The Sjöberg Foundation, Swedish Research Council, Swedish Cancer Society.

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9534 **Poster Session**

Phase 1b trial of IFx-Hu2.0, a novel personalized cancer vaccine, in checkpoint inhibitor resistant merkel cell carcinoma and cutaneous squamous cell carcinoma.

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Background: Merkel cell carcinoma (MCC) and cutaneous squamous cell carcinoma (cSCC) exhibit high response rate to immune checkpoint inhibitor (ICI) therapy. However, patients with advanced disease who fail initial ICI therapy have limited treatment options. IFx-Hu2.0 (IFx) is a plasmid DNA encoding for an immunogenic bacterial protein, Emm55, formulated with a transfection agent for direct intratumoral injection. In a phase 1 study in advanced melanoma, biomarker analyses demonstrated robust immune priming effects of IFx administration. As part of an ongoing Phase 1b study, we evaluated the safety and immunologic response of different schedules of IFx intratumoral administration in patients with advanced MCC or cSCC. We report the initial results of the first stage of this study. **Methods:** In the first trial stage (n = 9), IFx was administered intratumorally in up to 3 lesions on 3 schedules; weekly x 1, 2, or 3. We report safety data for these patients. Given the proposed potential for immune priming effects of IFx, we performed an unplanned exploratory analysis of post-protocol treatment efficacy to evaluate for response to ICI rechallenge if given. **Results:** Five patients with advanced MCC and four with cSCC were enrolled. Prior to trial enrollment, all patients with MCC received ICI with pembrolizumab (4) or avelumab (1), all had progressive disease with median 3 months treatment (2.0-4.5mo). All 4 patients with cSCC previously received cemiplimab with median 6 months treatment (3.0-11.5mo). IFx was well tolerated at all dose schedules evaluated with no treatment-related G3-5 adverse events observed. Best response to trial therapy was SD in 2 patients and PD in seven. One MCC patient experienced complete clinical response in 2 injected lesions, but progression of disease overall with development of new disease areas. Following completion of protocol therapy, all 5 MCC patients and 2 of 4 cSCC patients were treated with anti-PD(L)1 therapy as the immediate post-protocol therapy: pembrolizumab (3) or avelumab (2) in MCC and cemiplimab (2) in cSCC. Four of 5 MCC patients and 1 of 2 cSCC patients, or 5 of 7 total (71%), experienced objective response to ICI rechallenge in this setting, with duration of response ongoing in 4 patients (7+, 8+, 9+, 20+ months) and one response lasting 23 months. **Conclusions:** IFx-Hu2.0 is safe and well tolerated at weekly dosing repeated up to 3 weeks. An exploratory analysis showed that five of seven patients (71%) treated with standard of care ICI agents following protocol therapy experienced a durable objective response despite prior failure of this same drug class prior to protocol enrollment. An additional 11 patients are planned for enrollment in the expansion stage of the study using the weekly x3 dosing schedule. Preliminary biomarker analyses from the first nine patients are ongoing and will be presented. Clinical trial information: NCT04160065. Research Sponsor: Morphogenesis, Inc.

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9535 **Poster Session**

Updated results from an ongoing phase 1/2a study of T3011, an oncolytic HSV expressing IL-12 and PD-1 antibody, administered via IT injection as monotherapy or combined with pembrolizumab in advanced solid tumors.

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Background: T3011 is a recombinant HSV-1 oncolytic virus expressing both IL-12 and anti-human PD-1 antibody. Upon injection, locally produced IL-12 induces IFN-γ production, enhances the oncolytic activity of NK cells and cytotoxic T lymphocytes, promotes anti-angiogenesis and inhibits tumor growth. PD-1 antibodies act as immune checkpoint inhibitors to augment tumor-killing activity of T-cells. Here we report the updated results from an open-label, dose escalation and expansion study of T3011 administered via intratumoral injection as monotherapy or in combination with intravenous pembrolizumab. **Methods:** Pts with pathologically confirmed recurrent or metastatic malignancy after failure of SOC were enrolled and received T3011 monotherapy ($1*10^6$-$5*10^7$ PFU/mL Q2W) or in combination with pembrolizumab (Lead-in T3011 $1*10^6$ PFU/mL Q2W monotherapy for 2 cycles followed by combination therapy Q3W). Pts with documented progression on T3011 monotherapy may cross over to receive combination therapy at the discretion of the investigator. The primary endpoints were safety and tolerability. Key secondary endpoints included confirmed ORR, DCR, DOR, PFS by investigator per RECIST1.1; OS; PD and PK. **Results:** As of 17 Jan 2023, 29 pts received T3011 alone or in combination with pembrolizumab, the median follow-up was 14.1 (1.2-27.6) months. No DLTs were reported. Any treatment-related adverse events (TRAEs) occurred in 75.9% (22/29) of pts (≥G3 in 10.3%). Treatment-related SAEs occurred in 3.4% (1/29). Most frequent TRAEs (≥10%) were pyrexia (27.6%), fatigue (20.7%) and chills, injection site pain, arthralgia, nausea, headache (10.3% each). No additional safety signals were observed with combination therapy. 12 advanced melanoma pts failing prior PD-1 or PD-1/CTLA-4 combination treatment received $5*10^7$ PFU/mL of T3011 monotherapy. The confirmed ORR and DCR were 25.0% (3/12) and 33.3% (4/12), respectively. 12-month PFS rate was 36.4%. 6 of these pts were re-challenged with immunotherapy with T3011 ($5*10^7$ PFU/mL) combined with pembrolizumab after progressing on T3011 monotherapy, 1 pt achieved PR after 4 months lasting > 8 months at data cutoff. 15 pts had tumor tissues for PD analysis. Increased CD8+ cells were observed in 46.7% (7/15) of all pts and 50% (5/10) of melanoma pts. It appeared to be more pronounced in pts with PR and SD, 66.7% (6/9) in all pts and 80% (4/5) in melanoma pts, respectively. Notably, the increment of CT8+ cells in 2 melanoma pts with PR was over 15 folds. **Conclusions:** Both T3011 IT monotherapy and combination therapy with pembrolizumab were safe and tolerable. The efficacy of T3011 in immune-resistant melanoma was encouraging. Our data suggest T3011 may modify the tumor microenvironment and overcome immune resistance. Clinical trial information: NCT04370587. Research Sponsor: Immvira Pharma Co., Limited.

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9536 **Poster Session**

Targeting AMP kinase in melanoma: A phase I trial of phenformin with dabrafenib/trametinib.

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Background: AMP-activated protein kinase (AMPK) can phosphorylate BRAF and block its activation of MEK. AMPK is activated by biguanides such as metformin and phenformin (phen). Preclinical data indicated that phen can enhance the effects of BRAF inhibitors (BRAFi) in sensitive and BRAFi-resistant melanoma (mel) cell lines whereas metformin does not. Phen also can decrease myeloid-derived suppressor cells (MDSCs) enhancing immune reactivity against mel. For these reasons, we designed a phase I trial combining phen with dabrafenib/trametinib (dab/tram) in patients (pts) with metastatic BRAF V600-mutated mel. **Methods:** Bulk phen was provided by the Division of Cancer Treatment and Diagnosis of the National Cancer Institute under a materials transfer agreement. Phen was encapsulated at the Pharmaceutical Product Facility at MSKCC under cGMP procedures and used under an IND held by MSKCC. Eligible pts had metastatic BRAF V600-mutated mel. For the dose-escalation phase, prior BRAFi therapy was allowed. A 3+3 dose escalation design was used starting at a phen dose of 50 mg bid and standard dosing of dab/tram (150 mg bid/2 mg qd). Subsequent planned dose levels were 100 mg bid, 200 mg bid, and 300 mg bid with de-escalation to intermediate doses for toxicity. Plasma PK samples were collected and assayed by MRI Global Inc using a validated, GLP-compliant, HPLC-MS/MS assay. PBMC were collected to measure circulating MDSCs. At the recommended phase 2 dose (RP2D), we planned to treat 10 BRAFi-naïve pts. **Results:** We accrued 18 patients from March 2017 through December 2019. Dose-escalation to 200 mg bid was not tolerable nor was 150 mg bid. Therefore, we determined 100 mg bid to be the RP2D and accrued 2 patients on the dose expansion cohort before further accrual became impossible due to the COVID-19 pandemic. The most common toxicities were gastrointestinal – nausea, vomiting, anorexia, and transaminase and alkaline phosphatase elevation – accounting for 9 DLTs. Two patients were hospitalized due to lactic acidosis. There were also constitutional/inflammatory and skin/mucosal adverse events thought to be related to dab/tram. Weight loss was seen in most patients (median 3.7% at week 8) thought to be related to phen. There were 8 PRs and 2 CRs. Responses were observed in 2/7 pts who had received prior therapy with BRAFi. One CR lasted $>$ 1 year. There were 8/11 (73%) responders among the BRAFi-naïve pts. At the RP2D of 100 mg bid, day 8 median phen plasma level was 73.4 ng/ml (range 32.8-253.2). At the the 50 mg bid dose level, it was 40.8 ng/ml (range 29.7-110.2). MDSC could be analyzed from the 150 mg bid and 200 mg bid dose levels (N = 7 pts). In all but 1 pt, MDSCs decreased while on phen. **Conclusions:** We observed 10/18 (55.5%) total responses with 2/7 among previously treated pts. Circulating MDSCs decreased on treatment. Phen at 100 mg bid can be combined safely with dab/tram and should be explored in future randomized phase II trials. Clinical trial information: NCT03026517. Research Sponsor: MSKCC; U.S. National Institutes of Health.

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9537 **Poster Session**

Avelumab as second-line or later (2L+) treatment in patients (pts) with metastatic Merkel cell carcinoma (mMCC): Analysis of real-world outcomes in France using the CARADERM registry and the French national healthcare database.

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Background: Avelumab, an anti–PD-L1 antibody, has been approved in multiple countries for the treatment of mMCC based on the results of the pivotal phase 2 JAVELIN Merkel 200 trial (NCT02155647). In pts who received avelumab as 2L+ treatment in the trial (part A), median overall survival (OS) was 12.6 months and median progression-free survival (PFS) was 2.7 months. The French health technology assessment agency requested the collection of real-world data from pts with mMCC from a comprehensive registry; data are reported here. **Methods:** This retrospective, noninterventional, real-world study evaluated all pts with mMCC in France using combined data from 2 databases: CARADERM (French national database of rare dermatological cancers) and Système National des Données de Santé (SNDS; national healthcare database). For this analysis, eligible pts were diagnosed with mMCC and initiated 2L+ avelumab outside of a clinical trial between August 2016 and December 2019. Pts were followed for 24 months after initiation of avelumab. Probabilistic linkage was performed to identify pts registered in both databases. OS and PFS were analyzed using Kaplan-Meier methodology. Safety data were not collected. **Results:** A total of 180 pts who received 2L+ avelumab were identified, data were obtained for 112 pts from the CARADERM database and for 68 additional pts after SNDS linkage. Median age at diagnosis was 74.0 years, 66.7% were male, and 98.3% received chemotherapy as first-line treatment. Median follow-up was 13.1 months. 79.5% of CARADERM database pts had discontinued avelumab; the most common reasons specified were progressive disease (36.4%), complete response (17.0%), and death (13.6%). Median OS was 14.6 months (95% CI, 9.9-21.3 months) overall; in CARADERM database pts, median OS was 15.9 months (95% CI, 8.6-28.3 months) vs 13.3 months (95% CI, 6.7-19.1 months) in non-CARADERM database pts. 12- and 24-month OS rates in the overall population were 53.8% (95% CI, 46.2%-60.8%) and 40.5% (95% CI, 33.2%-47.6%), respectively. In CARADERM database pts (data not available in non-CARADERM database pts), median PFS was 3.6 months (95% CI, 2.7-7.5 months), and the objective response rate was 55.3% (95% CI, 45.3%-65.4%), including complete response in 31.9%. Median duration of response was 39.3 months (95% CI, 24.3 months-not estimable). **Conclusions:** In this real-world study of national data from France, outcomes with avelumab as 2L+ treatment for mMCC were similar to those observed in part A of the JAVELIN Merkel 200 trial. These findings confirm the effectiveness of avelumab in pts with mMCC that have progressed following first-line systemic treatment in routine clinical practice. Research Sponsor: This study was sponsored by Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

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9538 **Poster Session**

Immune infiltrates in metastatic uveal melanoma liver metastases and associations with clinical outcomes.

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Background: Uveal melanoma has a poor prognosis following metastasis to the liver. Immune checkpoint inhibitors (ICIs) are often utilized in patients with metastatic uveal melanoma (MUM); however, ICIs in MUM have low response rates. We studied the association of immune infiltrates in MUM liver metastases with survival outcomes for all patients, in addition to evaluating if immune infiltrates improve survival for patients treated with ICIs. **Methods:** We included MUM patients with liver metastases who had pre-treatment liver biopsies available at Mayo Clinic Rochester. Demographics, disease characteristics, treatments, and clinical outcomes were obtained from the electronic medical record. Core biopsies of liver metastases were reviewed for the presence of lymphocytes at interface of the tumor and liver parenchyma, and for tumor-infiltrating lymphocytes (TILs). If TILs were present, then additional immunohistochemistry (IHC) staining was performed for CD3, CD4, CD8, PD1, CD25, and FoxP3. Overall survival (OS) was estimated with the Kaplan-Meier method and compared between groups with Cox proportional hazards regression. Median OS and hazard ratios (HR) were calculated and p-values (p) <0.05 were considered statistically significant. **Results:** 140 patients with MUM who had pre-treatment liver biopsies were identified. 122 biopsies were evaluable for the presence of lymphocytes, either at the tumor-liver interface, or for TILs. 80/122 (65.6%) biopsies showed presence of any lymphocyte and 27/80 had TILs. 27 biopsies had sufficient tissue for further IHC classification. CD8+ T cells were identified in 27/27 samples, T cell PD1 positivity $\geq$1% in 4/27 samples, and regulatory T cell markers (CD25 and/or FoxP3) in 18/27 samples. Median OS for the entire cohort was 16 months (mo). Patients still alive at the time of data analysis had at least one year of follow-up available (range 13-124 mo). Univariate analyses (UVA) showed no significant improvement in OS based on the presence of any lymphocytes (HR 1.01, p 0.98), lymphocytes at the tumor-liver interface (HR 1.10, p 0.64), TILs (HR 0.78, p 0.27), $>$50% CD8+ T cells (HR 0.88, p 0.77), or absence of FoxP3+ T cells (HR 0.68, p 0.40). In the 69 patients treated with ICIs (pembrolizumab, nivolumab, or ipilimumab plus nivolumab), neither the presence of any lymphocytes (HR 1.19, p 0.56) nor TILs (HR 0.68, p 0.24) were associated with an OS benefit. **Conclusions:** We present a large cohort of patients with MUM where we characterized immune infiltrates in liver metastases and evaluated clinical outcomes. OS did not significantly improve with the presence of any lymphocytes, TILs, CD8+ T cells, or with the absence of FoxP3+ T cells. These results were consistent across all patients whether they were treated with ICIs or not. Our findings suggest that lymphocytes in MUM are functionally dormant and highlights the need for novel immune-activating treatment strategies. Research Sponsor: Mayo Clinic.

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9539 **Poster Session**

Economic evaluation for the US of relatlimab and nivolumab (RELA+NIVO) versus nivolumab (NIVO) monotherapy in untreated advanced melanoma.

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Background: The RELATIVITY-047 trial demonstrated longer median progression-free survival (PFS) with the combination of RELA+NIVO (10.1 months, 95% CI = 6.4 to 15.7) over NIVO (4.6 months, 95%CI = 3.4 to 5.6) in patients with untreated advanced melanoma (hazard ratio for progression or death = 0.75, 95%CI = 0.62 to 0.92). This economic evaluation aimed to estimate the cost-effectiveness/utility of RELA+NIVO vs. NIVO monotherapy in this setting. **Methods:** A two state partitioned survival model (PFS, progressed/death) was developed to compare costs and PFS outcome associated with both treatments. PFS curves were digitized and parametric functions fitted. A 5-year time horizon from a US payer perspective with a 3% discount rate/year was considered. Costs of treatment (average sales price), administration and monitoring parameters were derived from Centers for Medicare & Medicaid Services databases; cost of adverse events (grade 3/4 with rate >5%) were derived from prior advanced melanoma economic evaluations. Incremental costs, PFS life years (PFSLY), and PFS quality adjusted life years (PFSQALY) gained (g) were estimated in base case (BCA) and probabilistic sensitivity analyses (PSA). A cost-effectiveness acceptability curve (CEAC) was plotted to determine the probability of either treatment to be cost-effective over the other at different willingness to pay (WTP) thresholds. **Results:** Exponential regression was used to extrapolate RELA+-NIVO and NIVO survival curves. According to the result table shown below, the BCA (PSA) shows an incremental cost of RELA+NIVO over NIVO of $405,663 ($402,936), incremental PFSLY of 0.326 (0.325), and incremental PFSQALY of 0.260 (0.256). The BCA (PSA) ICERs indicated an additional $1,244,365 ($1,239,803) per PFSLY gained (g) and an additional $1,560,242 ($1,573,969) per PFSQALYg. The CEAC curve shows that RELA+NIVO treatment had a 50% probability of being cost-effective regimen at a WTP threshold value of $1,525,000 and 100% probability at a threshold of $3,050,000 or above. **Conclusions:** In the setting of advanced melanoma, this economic evaluation showed that RELA+NIVO is associated with improvement in LY and QALY, however, at a marked incremental cost, requiring a very high WTP threshold. Research Sponsor: None.

BCA (PSA).

	RELA+NIVO	NIVO	Difference
Cost	$682,148 ($679,432)	$276,485 ($276,496)	$405,663 ($402,936)
PFSLY	1.673 (1.665)	1.347 (1.340)	0.326 (0.325)
PFSQALY	1.338 (1.331)	1.078 (1.075)	0.260 (0.256)
ICER			$1,244,365/PFSLYg ($1,239,803/PFSLYg)
ICUR			$1,560,242/PFSQALYg ($1,573,969/PFSQALYg)

Interpretation of ICER and ICUR: incremental cost to gain resp. 1 LY or 1 QALY.

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9540 **Poster Session**

Interim results from a phase I/II study of duvelisib PI3Kδγ inhibitor and nivolumab in patients with advanced unresectable melanoma who have progressed on anti-PD1 therapy.

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Background: The majority of unresectable melanoma patients eventually progress on first-line checkpoint blockade therapy. Duvelisib is a potent phosphoinositide 3-kinase (PI3K) δ and γ isoform inhibitor approved for relapsed/refractory CLL. PI3Kγ inhibition has been shown to restore anti-PD1 activity in preclinical tumor models through conversion of tumor associated macrophages (TAMs) from an immunosuppressive to a pro-inflammatory state. PI3Kδ inactivation has been associated with impaired T regulatory cell (Treg) function and reduced intratumoral Treg numbers. We report study design and results of a phase I study to evaluate the safety and efficacy of duvelisib and nivolumab in anti-PD1 refractory patients. **Methods:** Utilizing a modified 3+3 design with escalating doses of duvelisib (15 mg daily, 25 mg daily, and 25 mg BID), patients with unresectable melanoma were treated with nivolumab and duvelisib until unacceptable toxicity or disease progression. Primary endpoints for the phase I portion were maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of duvelisib. Secondary endpoints include early and late toxicities and anti-tumor activity based on RECIST v1.1. Exploratory endpoints were to evaluate dose-dependent changes in the immune cell populations of peripheral blood and tumor tissue with duvelisib and nivolumab. **Results:** Ten patients have been enrolled (7 at dose level I, 3 at dose level II) with mean age 64. Two patients had BRAF V600E mutation and were previously treated with BRAF/MEK inhibitors. No dose limiting toxicities (DLT) were observed. Grade 3 or higher adverse events (AEs) attributable to study treatment occurred in 4 patients (40%), including G3 neutropenia (10%), G3 diarrhea (10%), G3 vomiting (10%) and G4 hepatitis (20%). Both instances of hepatitis resolved rapidly with 1-2mg/kg of prednisone. In one patient, hepatitis and nausea/vomiting led to discontinuation of treatment. Out of 6 patients who had follow-up imaging, 4 exhibited progressive disease, one stable disease, and one had partial response of 11 months duration. Given the published data on the regulation of macrophages and Tregs by PI3Kδγ inhibitors, we are utilizing multispectral imaging to measure the spatial interactions of key immune cells within the tumor microenvironment (T cells, B cells, and macrophages) in all matched pre-/post-treatment paraffin-embedded tissues, for which results will be presented. **Conclusions:** The combination of duvelisib and nivolumab was well-tolerated in patients with advanced unresectable melanoma refractory to ICI without DLTs to date at 15 and 25mg daily dosages. Significant anti-tumor activity was noted in one patient. Enrollment at dose level II is ongoing. Clinical trial information: NCT04688658.
Research Sponsor: Secura Bio, Inc.

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9541 **Poster Session**

Updated safety and efficacy results from the phase I study of either LBL-007 (an anti-LAG-3 antibody) in combination with toripalimab (an anti-PD-1 antibody) or LBL-007 in combination with toripalimab and axitinib in patients with advanced melanoma.

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Background: Initial safety and efficacy data of LBL-007 plus toripalimab in patients with advanced melanoma (Part A) have been reported in 2022 ASCO (Abstract 9538). Here we present the updated results of part A and the preliminary results of part B (LBL-007 plus toripalimab with axitinib). Median follow-up was 9.7 months at cut-off data (January 11, 2023). **Methods:** Patients with advanced melanoma with or without prior therapy were enrolled during Jan 2021 - Aug 2022. This trial comprised 2 parts: Part A, patients received LBL-007 (0.25 - 10 mg/kg for dose escalation; 3 or 6 mg/kg for dose expansion) plus toripalimab at 3 mg/kg (both i.v. Q2W); and Part B, patients received LBL-007 at 3 or 6 mg/kg plus toripalimab at 3 mg/kg (both i.v. Q2W) and axitinib at 5 mg BID. The primary objective was safety, the second objectives were pharmacokinetics, pharmacodynamics and efficacy (per RECIST v.1.1). **Results:** In part A, 68 patients in total (57 treatment-naïve) were enrolled including 20 patients in dose escalation and 48 patients in dose expansion, and among which, 31 additional patients have been enrolled since 2022 ASCO report. Nineteen (27.9%) patients occurred grade ≥3 TEAEs, the common grade ≥3 TEAEs was anaemia (11.8%). No new safety signals were detected. Among 55 efficacy evaluable treatment-naïve patients (41 with acral, 7 mucosal, 7 others), ORR was 23.6%, DCR was 58.2%, and mPFS was 5.7 months (95% CI: 3.7, 9.5). In part B, 11 patients (10 mucosal, 1 acral) were enrolled. No DLT was observed. Five patients (45.5%) occurred grade ≥3 TEAEs, the common grade ≥3 TEAEs included blood pressure increased (18.2%) and transaminases increased (18.2%). One (9.1%) patient discontinued treatment due to TEAEs. ORR was 45.4% (including 4 mucosal and 1 acral), DCR was 72.7%, and mPFS was 5.5 months (95% CI: 1.8, 9.1). **Conclusions:** LBL-007 plus toripalimab continued to show promising antitumor activity and manageable safety profile in patients with treatment-naïve melanoma, which support further development in this indication. LBL-007/toripalimab/axitinib combination demonstrated acceptable safety profile and encouraging antitumor activity in patients with mucosal melanoma. Acknowledgements: Junshi Biosciences. Clinical trial information: NCT04640545. Research Sponsor: Nanjing Leads Biolabs Co., Ltd.

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Durable clinical outcomes in patients (pts) with advanced melanoma and progression-free survival (PFS) ≥3y on nivolumab (NIVO) ± ipilimumab (IPI) or IPI in checkmate 067.

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Background: NIVO + IPI has demonstrated durable clinical benefit at 7.5 y in pts with advanced melanoma in the phase 3 CheckMate 067 study. PFS curves plateaued at ~3 y in this study, suggesting that being alive and progression-free for ≥ 3 y (PFS ≥ 3y) may be a good surrogate for long-term clinical benefit. We conducted analyses to quantify this association. **Methods:** Pts with treatment (tx)-naive, unresectable stage III/IV melanoma (stratified by PD-L1 expression, *BRAF* mutation status, and metastasis stage) received NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W, followed by NIVO 3 mg/kg Q2W (n = 314); NIVO 3 mg/kg Q2W + placebo (n = 316); or IPI 3 mg/kg Q3W for 4 doses + placebo (n = 315) until progression or unacceptable toxicity. Exploratory post hoc analysis was performed in pts with PFS ≥ 3y. **Results:** In the NIVO + IPI, NIVO, and IPI arms, respectively, 99 (32%), 78 (25%), and 21 (7%) pts had PFS ≥ 3y. Objective response rates (ORRs) in these pts were ≥ 95% (table). The majority of responses were complete responses (CRs; table); in almost all pts with partial responses (PRs) on NIVO + IPI or NIVO, target-lesion size decreased by ≥ 50%. At 7.5 y of follow-up among pts alive and progression-free at 3 y, PFS rates were ≥ 68%, overall survival (OS) rates were ≥ 85%, and melanoma-specific survival (MSS) rates were ≥ 95% in the 3 tx groups (table). Among pts in this group who died after 3 y on study, the majority of deaths were unrelated to disease (table). The majority of pts with PFS ≥ 3y who were alive and in follow-up were tx-free at the 7.5-y data cutoff (77/84, 57/64, and 13/16). Pts who received NIVO + IPI were off tx (median) for 75.5 mo (NIVO, 55.7 mo; IPI, 59.2 mo). Among pts with PFS ≥ 3y in the 3 tx groups, 4%, 5%, and 19% received subsequent systemic tx (table). No new safety signals were observed in pts with PFS ≥ 3y. **Conclusions:** This exploratory post hoc analysis suggested that PFS ≥ 3y may be a good surrogate for long-term MSS with NIVO + IPI or NIVO, with very few occurrences of progression or death due to melanoma in this population through 7.5 y. Most pts were tx-free without having received subsequent systemic tx after demonstrating PFS ≥ 3y. Further study of pts with PFS ≥ 3y may allow the burden of imaging and follow-up visits to be reduced in this group. Clinical trial information: NCT01844505. Research Sponsor: Bristol Myers Squibb.

Outcomes at 7.5 y in pts with PFS ≥ 3y.

	NIVO + IPI (n = 99)	NIVO (n = 78)	IPI (n = 21)
ORR, % (95% CI)	100 (96–100)	99 (93–100)	95 (76– < 100)
Best overall response, n (%)			
CR	57 (58)	50 (64)	12 (57)
PR	42 (42)	27 (35)	8 (38)
Stable disease	0	1 (1)	1 (5)
PFS rate, % (95% CI)	84 (73–90)	85 (73–92)	68 (41–84)
Pts with PFS event after 3 y, n	13	11	6
MEL-unrelated deaths	7	3	2
OS rate, % (95% CI)	89 (80–94)	95 (87–98)	85 (60–95)
Deaths after 3 y, n	11	5	3
MEL-unrelated deaths	8	3	1
MSS rate, % (95% CI)	98 (92–99)	97 (89–99)	95 (68–99)
Subsequent tx, n (%)			
Any	12 (12)	12 (15)	7 (33)
Systemic	4 (4)	4 (5)	4 (19)
Radiotherapy	4 (4)	2 (3)	4 (19)
Surgery	10 (10)	9 (12)	3 (14)

MEL, melanoma.

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9543 **Poster Session**

The effect of LNS8801 alone and in combination with pembrolizumab in patients with metastatic uveal melanoma.

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Background: LNS8801 is an oral, selective, small molecule agonist of the G-protein coupled estrogen receptor (GPER). LNS8801 treatment results in increased melanocytic differentiation, reduced c-Myc protein levels in cancer cells, inhibition of proliferation, suppression of invasion, and enhancement of immune recognition. In preclinical models, LNS8801 has demonstrated increased activity in combination with immune checkpoint inhibitors (ICIs). In the first-in-human dose escalation study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab in patients with advanced solid tumors (NCT04130516). **Methods:** Patients with measurable metastatic uveal melanoma (mUM) received LNS8801 (125 mg, QD, PO) alone or with pembrolizumab (200 mg, Q3W, IV) (NCT04130516). The primary objective was safety and tolerability assessed according to NCI CTCAE v5.0. Secondary endpoints include pharmacokinetic, pharmacodynamics, objective response rate (ORR) and disease control rate (DCR, CR+PR+SD) per RECIST v1.1. Presence of a consensus, fully-functional, germline GPER coding sequence was assessed via Sanger sequencing on DNA extracted from blood as a potential predictive biomarker. **Results:** As of 1/25/23, 15 patients with mUM were treated with LNS8801 alone (n = 8) or a combination of LNS8801 and pembrolizumab (n = 7). Patients were previously treated with a median of 2 prior lines of systemic therapy. 4 of 8 monotherapy patients had AEs potentially related to study drug (all grade 1), with no AEs occurring in more than one patient. 6 of 7 combination patients had AEs potentially related to study drugs (grades 1-2), with fatigue occurring in more than one patient. Of the 14 patients evaluable for efficacy (7 mono, 7 combo), 7 had disease control (4 mono, 3 combo) resulting in a disease control rate of 50%. 1 patient treated with combination achieved a confirmed partial response. Consensus germline GPER was present in 2 of 12 sequenced patients (1 mono, 1 combo), and both of these patients have ongoing disease control lasting longer than 24 weeks. **Conclusions:** LNS8801 alone and in combination with pembrolizumab is tolerable without unanticipated toxicities and demonstrates encouraging anti-tumor activity in patients with mUM. The hypofunctional germline GPER variant appears over-represented in this cohort compared to the normal population, suggesting a potential significant role for GPER in the development of mUM. These data support further development of LNS8801 alone and in combination with pembrolizumab as a therapeutic approach to treat mUM patients, especially for patients with consensus germline GPER. Clinical trial information: NCT04130516. Research Sponsor: Linnaeus Therapeutics.

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9544 **Poster Session**

Breaking primary checkpoint inhibitor resistance: Interim analysis of a multicenter phase II study by intermittent application of an alkylating agent among patients with metastatic melanoma.

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Background: Patients with *BRAF* wildtype (wt) metastatic melanoma with primary resistance to immune checkpoint inhibitors (ICI) have a dismal prognosis. Chemotherapy has been shown to induce mutations, alter the tumor microenvironment as well as the microbiome, and modulate the immune system. This prospective phase II trial investigates whether two applications of an alkylating agent (dacarbazine/DTIC) can render ICI non-responsive patients with metastatic melanoma responsive to the same checkpoint inhibitor regime. **Methods:** The PROMIT trial (NCT04225390) targets patients with histologically confirmed *BRAF*wt metastatic melanoma showing primary resistance to ICI therapy. Applying an optimal two-step design, the uninteresting responder rate was set to 5% with an expected rate of 20%. Response is defined as complete or partial response by week 14 according to RECIST 1.1. Design foresaw 29 assessable patients at first step and 38 patients overall (alpha one-sided 5%, 90% power).After showing primary resistance to ICI, patients received 2 doses of DTIC (850 mg/m^2 i.v.) on days 1 and 21, and were subsequently re-exposed to the same ICI therapy they had previously shown resistance to. **Results:** In total, 38 patients were screened at 4 skin cancer centers. Interim analysis was performed after 29 patients who had received at least one ICI re-exposure were assessable for efficacy. Overall response rate was 24% (90%CI 12-41%) with 7 out of 29 patients showing a partial response; disease control rate was 38%. Application was well tolerated with 16% grade 3 or more adverse events and no new safety signals. **Conclusions:** Interim analyses results indicate that this approach of a short-term chemotherapy can break resistance in a subgroup of patients and allows us to continue the phase II trial to assess relevance of this treatment approach for metastatic melanoma. Enrolment is ongoing. Clinical trial information: NCT04225390. Research Sponsor: German Cancer Aid; University hospitals.

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9545 **Poster Session**

Real-world comparison between 6 weeks versus 3 weeks adjuvant pembrolizumab in high-risk stage IIB-IIID cutaneous malignant melanoma: Experience from an academic cancer center.

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Background: The KEYNOTE-555 trial demonstrated similar efficacy and safety profile of 6-week (q6w) pembrolizumab (400 mg/m^2) vs 3-week (q3w) in unresectable and metastatic melanoma leading to FDA's approval of this dosing schedule for adults in 2020. Limited real-world data is available on the use of 3 weeks vs 6 weeks pembrolizumab in the adjuvant setting in cutaneous melanomas. Q6w is hypothesized to cause more adverse effects due to higher drug concentration. **Methods:** We conducted a retrospective study of surgically resected Stage IIB-IIID cutaneous melanomas receiving adjuvant pembrolizumab from 2019-2022 at The James Comprehensive Cancer Center with a follow-up of ~1 year. Fifty patients [n=35 (q6w) and n=15 (q3w)] were included. The primary objectives were to compare disease free survival (DFS) and safety profile based on the NCI-CTCAE (v 5.0) criteria. Kaplan-Meier curves were generated for DFS comparisons between the two groups. Fisher's exact test was used to compare the safety profile between the two groups. Accuracy of the sample size for final analysis was planned based on log rank test. With 15 patients (q3w) and 35 patients (q6w), our study had 80% power to detect differences in clinical outcomes. A p-value of less < 0.05 was considered statistically significant. The secondary objective was to compare overall survival (OS) which will be reported later with a longer follow-up. **Results:** The mean age in the q6w and q3w groups was 59 years and 69 years, respectively. The median follow up was ~ 9 months with males predominating in both groups (54% and 18%). In the q6w group, 68% had ECOG status 0 (vs.30% in q3w) and most of our patients (32%) were stage IIIB (vs. 6% in q3w) and 28% were stage IIIC (vs 12% in q3wk). *BRAF* mutation was present in 32% in q6w vs. 2% in q3w. Toxicity profile was noted to be similar in both groups with no significant statistical difference (p-value=0.4), though there were more Grade-3 immune-related toxicities in 7 patients in the q6w group (vs 3 in q3wk). The most common grade 3 toxicity noted was colitis (n=4, q6w; n=1, q3w). Notably, no significant difference was noted in the DFS between the two groups (p-value=0.6). At the time of analysis, 3/15 (20%) patients in q3w and 7/35 (20%) in the q6w group had disease progression with the most common site being the regional lymph-nodes. At the time of the last follow up, 96% of the patients were alive with only 2 deaths occurring due to non-cancer related causes. **Conclusions:** We demonstrate comparable efficacy of q6w and q3w adjuvant pembrolizumab for advanced stage melanoma, with a trend towards increased immune-mediated colitis events in q6w. Research Sponsor: None.

Characteristics		q6w n=35(%)	q3w n=15(%)
Age (years)		59 (21-87)	69 (54-84)
Gender	Male	19 (54)	9 (60)
	Female	16 (46)	6 (40)
TNM stage	II B-C	-	5
	III A-D	35 (100)	10 (66.67)
Colitis	Grade 1-2	2	0
	Grade 3	4	1
Fatigue	Grade 3	1	1
Hepatitis	Grade 3	1	1

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Neoadjuvant T-VEC + nivolumab combination therapy for resectable early metastatic (stage IIIB/C/D-IV M1a) melanoma with injectable disease: NIVEC trial.

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Background: Neoadjuvant systemic treatment with checkpoint inhibitors (ICI) has shown high response rates in patients with resectable metastasized melanoma. In patients with unresectable stage IIIB-IVA melanoma, intralesional treatment with talimogene laherparepvec (T-VEC) has also shown high and durable response rates. In this trial we investigated the safety and efficacy of neoadjuvant treatment with a combination of nivolumab and T-VEC in regionally metastasized melanoma. **Methods:** In this single arm phase II open-label trial (NCT04330430), 24 patients with resectable stage IIIB-IVA melanoma were included. Inclusion criteria were a RECIST 1.1 measurable lesion of $\geq$10mm and no prior systemic therapy. Treatment consisted of four doses of intralesional T-VEC (dose in ml according to the size of the lesions) and three doses of nivolumab 240 mg flat dose every two weeks, followed by surgery. The primary endpoint was pathological response rate according to the International Neoadjuvant Melanoma Consortium (INMC) criteria, secondary endpoints were delay or failure to perform surgery, event free survival (EFS) from time of randomization and safety. **Results:** Baseline characteristics are presented in the table. The overall pathological response rate was 74%, with a major pathological response (MPR = pathologic complete response (pCR) + near-pCR (max 10% viable tumor cells) in 15 patients (65%), a partial response in two patients (9%), a non-response in 4 patients (17%) and progression of disease (PD) in two patients (9%). In one patient the response was not evaluable because surgery was delayed due to a vena cava thrombosis. The two patients with PD had evidence of distant metastasis on preoperative imaging and therefore did not proceed to surgery as planned. Grade 2 treatment related adverse events (trAE) occurred in 7 patients (29%) and grade 3 in 2 (8%). There were no grade 4-5 trAEs. The 1-year EFS was 75% (95%CI 0.55-1). **Conclusions:** Neoadjuvant combination therapy of nivolumab and T-VEC for patients with regionally metastasized melanoma (satellite/in-transit +/- lymph node metastases) has an acceptable toxicity profile and has shown a significant major pathological response rate of 65%. Clinical trial information: NCT04330430. Research Sponsor: AMGEN.

Baseline characteristics of patients included in NIVEC trial.

	All patients (n=24)
Gender	
- Male	13 (54%)
- Female	11 (46%
Age (median, IQR)	67 (56-73)
WHO performance score	
- 0	23 (96%)
- 1	1 (4%)
Stage	
- IIIB	14 (58%)
- IIIC	8 (33%)
- IIID	2 (9%)
BRAF status	
- Positive	11 (46%)
- negative	13 (54%)
Number of lesions (mean)	2.2 (2 unknown*)
Maximum diameter target lesion (median, IQR)	22 mm (18-34)(2 unknown*)

*Revision pending.

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9547 **Poster Session**

Retreatment and rechallenge with BRAF/MEK inhibitors in patients with metastatic melanoma: Results from the observational study GEM1801.

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Background: Most patients with BRAF-mutant melanoma eventually develop resistance to therapy with BRAF/MEK inhibitors and immune-checkpoint blockade. Alternative treatment strategies are required in these patients since further therapy options lack survival benefit. Small series have shown promising activity from re-exposure to BRAF/MEK inhibitors after a treatment free interval of targeted therapy (TT), probably due to regression of resistant tumors and proliferation of clones that maintain sensitivity to BRAF/MEKi. However, prospective evidence for this approach is limited. Here we report the results of 30 patients who received a second course of TT at relapse after adjuvant therapy (retreatment) or after first progression on TT in the advanced setting (rechallenge). **Methods:** GEM1801 is a prospective observational study from the Spanish Melanoma Group (GEM) including 893 patients with melanoma treated in 37 centers. This is a descriptive analysis of basal characteristics, response rates (RR), progression free survival (PFS) and overall survival (OS) from 30 patients that received retreatment or rechallenge with BRAF/MEKi in GEM1801 study. **Results:** 4 patients received retreatment and 26 rechallenge. For retreatment, BRAF/MEKi median free interval from end of adjuvant TT to subsequent retreatment was 17.8 months (range: 12.4 - 57.7). RR with retreatment were 25%, with a median PFS and OS of 5.7 and 8.5 months. For rechallenge, RR was 38.5% and median PFS and OS 11.1 and 22.2 months respectively. Patients who were selected for rechallenge had higher complete response (CR) rates to first TT (26.9% vs 20.3%; *p= 0.026*). Patients who experimented deeper responses with 1st TT in the metastatic setting showed a correlation to longer PFS to 2nd TT with 12-m PFS rates of 66.7% versus 35.7% (HR 9.09 [95%CI: 1.42-58]; *p= 0.02*). OS showed a not statistically significant improvement in patients who reported CR to first TD (24-m OS rate of 75% versus 40.7% respectively). BRAF/MEKi free interval since first progression and retreatment or rechallenge was not associated with prognosis. Prognostic factors as LDH and number of metastatic sites did not correlate with the efficacy of retreatment. **Conclusions:** Retreatment or rechallenge with BRAF/MEKi in the metastatic setting achieved encouraging efficacy and may be a valid therapeutic strategy in a selected group of patients. Response to first treatment, retreatment and rechallenge with BRAF/MEKi. Clinical trial information: NCT03605771. Research Sponsor: GEM through industry partners: Novartis, Pierre Fabre, Incyte, BMS, Roche and MSD.

	First treatment N = 245		Retreatment (after adjuvant) N = 4		Rechallenge (after metastatic) N= 26	
	n	%	n	%	n	%
Complete Response	45	18.4	0	0	4	15.4
Partial Response	89	36.3	1	25	6	23.1
Stable Disease	33	13.5	0	0	3	11.5
Progression Disease	25	10.2	2	50	6	23.1
Not Evaluable	53	21.6	1	25	7	26.9
ORR	134	54.7	1	25	10	38.5
DCR	167	68.2	1	25	13	50

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9548 **Poster Session**

A phase 1 study of fianlimab (anti-LAG-3) in combination with cemiplimab (anti-PD-1) in patients with advanced melanoma: Poor-prognosis subgroup analysis.

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Background: Co-blockade of LAG-3 improves the effectiveness of anti-PD-1 treatment (Tx) in advanced melanoma (Mel) patients (pts). We previously reported high clinical activity of the combination immunotherapy of anti-LAG-3 (fianlimab) and anti-PD-1 (cemiplimab) in pts (N = 80) with anti–PD-1/PD-ligand (L)1-naïve advanced Mel enrolled in two expansion phase 1 cohorts. The objective response rate (ORR) (N = 80) and disease control rate (DCR) was 63.8% and 80.0%, respectively with median duration of response (mDOR) not reached (NR). Factors associated with poor prognosis include elevated lactate dehydrogenase (LDH) levels and sites of metastases, including liver or other visceral organs (M1c). Here we present updated efficacy data in poor prognosis pts from three phase 1 advanced Mel expansion cohorts: cohort 6 and 15 of anti-PD-(L)1/systemic Tx-naïve pts and cohort 16 of pts previously exposed to adjuvant (adj) or neo-adj systemic Tx including anti-PD-1. **Methods:** Pts with advanced Mel (excluding uveal Mel) were treated with fianlimab 1600 mg + cemiplimab 350 mg intravenously every 3 weeks for 12 months (+ additional 12 months if clinically indicated). Tumor measurements were assessed by RECIST 1.1 every 6 weeks for 24 weeks, then every 9 weeks. **Results:** 40 pts each in cohort 6 and 15, and 18 pts in cohort 16 (total N = 98) were enrolled and treated with fianlimab + cemiplimab as of 01 Nov 2022 data cutoff. In the adj/neo-adj setting, 23.5% of pts had received prior systemic Tx for Mel including 15.3% with prior exposure to immune checkpoint inhibitors (iCPIs). Median follow up was 12.6 months and median Tx duration was 32.9 weeks. ORR among all 98 pts and in 15 pts with prior iCPIs was 61.2% and 60.0%, respectively. In pts with LDH $>$ upper limit of normal (ULN) (N = 32, 32.7%), ORR, DCR, and mDOR were 53.1%, 71.9%, and NR (95% CI, 7.4– not estimated [NE]), respectively, and median progression-free survival (mPFS) was 11.8 months (95% CI, 3.7–NE). In pts with liver mets at baseline (BL) (N = 21, 21.4%), ORR, DCR, and mDOR were 42.9%, 57.1%, and 9.0 months (95% CI, 2.8–NE), respectively, and mPFS was 4.2 months (95% CI, 1.2–NE). In pts with any M1c disease and LDH $>$ ULN at BL (N = 17, 17.3%), ORR, DCR, mDOR were 35.3%, 58.8%, and NR (95% CI, 5.7–NE), respectively, and mPFS was 7.1 months (95% CI, 1.2–NE). Overall, 43.9% and 32.7% of pts reported grade $\geq$3 Tx-emergent adverse events (TEAEs) and serious TEAEs. Correlative biomarkers analyses are in progress and will be included in the presentation. **Conclusions:** The combination of fianlimab and cemiplimab showed high activity in pts with advanced Mel and poor prognosis features at BL. The ORR and DCR observed in these subgroups compare positively with the available data for approved combinations of iCPIs in the same clinical setting. A phase 3 trial (NCT05352672) of fianlimab + cemiplimab in Tx-naïve advanced Mel pts is ongoing. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

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9549 **Poster Session**

Determinants of racial disparities in immune-related adverse events (irAE) with checkpoint inhibition (ICI) in melanoma.

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Background: We recently reported that a pretreatment autoantibody (AutoAb) signature predicts immune-related adverse events (irAE) with an AUC of ~0.80 in melanoma patients enrolled in two phase III clinical trials of adjuvant ICI (Johannet *et al*. *CCR* 2022). The vast majority of those patients were non-Hispanic whites (NHW). We hypothesized that underrepresented minority (URM) melanoma patients might have a different baseline autoAb profile compared to NHW patients, as their site-specific irAEs differ (Xue Bai *et al*. *Br J of Derm* 2022) and autoimmune disease is generally more common in underrepresented minorities (Roberts MH, Erdei E. *Autoimmune Review* 2020). We also explored the possibility that differences in the immuno-biology of acral melanoma (AM) and cutaneous melanoma (CM) – most commonly detected in URM and NHW patients, respectively – might inform our understanding of the racial differences in irAEs. **Methods:** We compared pre-treatment sera autoAb from URM melanoma patients (n=35) to NHW patients (n= 185) enrolled in Checkmate-238 (NCT02388906), Checkmate-915 (NCT03068455) or the NYU melanoma program database using the CDI and Sengenics proteomic platforms, and analyzed their association(s) with the development of grade 3-4 irAEs. We carried out single cell RNA-seq in AM versus CM tumor tissues to test whether expression of genes whose proteins were associated with irAE were preferentially expressed in AM tissue. We also compared RNA-seq of an immunoregulatory gene panel in AM versus CM tumors. **Results:** We identified autoAbs that were only detected in sera from URM patients with grade 3-4 irAEs (e.g. *ALDOA, BANK1, LDHB* and *RNF7*) and autoAbs that were only detected in NHW patients with grade 3-4 irAEs (e.g. *GMEB2, YWHAE* and *ANKRD45*). A subset of these autoAb targets was preferentially expressed in AM or CM tissues, while other targets were undetected in these melanoma subtypes. Cytokine signaling pathways were enriched in sera from URM but not NHW patients, and expression of genes known to modulate irAEs and response to ICI were significantly more expressed in AM than CM tumors, e.g. *FOXP3* (P=0.01), *IL2* (P=0.00547), *IL4* (P=0.0221) and *IL10* (P=0.0126). **Conclusions:** Our data suggest that URM patients have an altered tumor immune microenvironment that defines their response to ICI and risk of developing irAE. An integrative analysis of both the tumor and systemic immune environments is needed to better understand molecular links between response to ICI and irAEs in URM and NHW melanoma patients. A multi-center study is planned to address these questions. Research Sponsor: U.S. National Institutes of Health.

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9550 **Poster Session**

Phase II clinical trial of camrelizumab combined with famitinib for advanced acral and mucosal melanoma.

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Background: Acral and mucosal melanoma were rarely seen in Caucasians but common in Asians. Previous studies revealed that acral and mucosal melanoma are more aggressive than cutaneous melanoma with a high unmet need for effective treatments. Camrelizumab plus anti-angiogenic agents have shown promising antitumor activity in previously untreated melanoma. Famitinib, a selective multiple-target tyrosine kinase inhibitor that exhibits both anti-angiogenesis and antiproliferative effects via targeting VEGFR-2, PDGFR, c-kit, FGFR and so on, combined with camrelizumab had been proven effective in multiple cancers. This study aimed to assess the antitumor activity and safety of camrelizumab plus famitinib in both immunotherapy naïve and experienced advanced mucosal or acral melanoma. **Methods:** This single-center, open-label phase II study recruited patients (pts) with advanced acral and mucosal melanoma. Pts who were immune checkpoint inhibitors (ICI) treatment naïve were in cohort 1, while pts experienced ICI in cohort 2. In both cohorts, pts received camrelizumab (200 mg i.v. q3w) and famitinib (20 mg po qd) until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) per RECIST1.1. Secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. This analysis focused on cohort 2. **Results:** As of January 12, 2023, 18 pts (9 mucosal and 9 acral histology subtypes) were enrolled in cohort 2. The median age of all pts was 58 yrs (ranged 38-71 yrs); 9 pts (50.0%) were female; prevalence of mutations: BRAF (11.1%), C-KIT or NRAS (16.7% each); 38.9% received $\geq$2 prior treatments. All pts progressed after anti-PD-1/L1 monotherapy (27.8%) or combinational therapy (66.7%), except one progressed after 4-1BB mAb monotherapy. The combination drugs included anti-LAG-3/CTLA-4 antibodies (38.9%), oncolytic viruses (11.1%), c-kit inhibitors, chemotherapy and anti-angiogenic agents (5.6% each). The median follow-up was 7.3 months (ranged 4.6-14.7 months). At the data cutoff, 5 pts remained on treatment. 17 pts were evaluable. The ORR and DCR were 17.6% and 64.7%, including two pts with confirmed PR, and one with unconfirmed PR, all of which were acral subtype. The median PFS was 6.0 months. The median OS was not reached. Of 18 pts, the incidence of treatment-related adverse events (TRAEs) was 88.9%. The most common grade 3 TRAEs was neutrophil count decreased (11.1%). No grade 4 TRAEs and no treatment-related deaths occurred. **Conclusions:** Camrelizumab plus famitinib showed promising antitumor activity in ICI-experienced advanced acral and mucosal melanoma pts, and was generally well tolerated. Clinical trial information: NCT05051865. Research Sponsor: None.

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9551 **Poster Session**

Final results: Dose escalation study of a personalized peptide-based neoantigen vaccine in patients with metastatic melanoma.

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Background: Despite the advances made with CPIs such as aPD-1/aPD-L1, aCTL4 and aLAG-3 there still is a significant unmet medical need for patients with metastatic cancers. As it has been shown that the effect of CPIs are mediated by tumor specific T cells, one strategy for increasing treatment success is to actively induce tumor specific T cells. Here, we report on a first-in-human clinical trial evaluating a personalized neoantigen vaccine (EVX-01) in patients with metastatic melanoma. **Methods:** Stage-IV metastatic melanoma patients were treated with standard aPD-1 in combination with a personalized tumor-specific neo-antigen vaccine. The vaccine consisted of multiple 15-27mer peptides comprising one or more patient specific neoantigens identified from tumor DNA and mRNA sequencing data by an integrated AI-platform; PIONEER and delivered together with the novel liposomal adjuvant CAF09b to potentiate immune responses. **Results:** Vaccines were designed and manufactured for each patient in less than 7 weeks. In total, 12 eligible patients received either 500ug (5 patients, reported in PMID: 35036074), 1000ug (3 patients) or 2000ug (4 patients) total peptide load keeping the peptide: CAF09b ratio constant. Four patients had stable disease on aPD-1 treatment for at least 4 months before enrolment in the study, whereas the remaining patients were treatment naïve. All patients received monotherapy with pembrolizumab (11) or nivolumab (1) during the vaccine manufacturing period. The personalized vaccine was shown to be safe and well tolerated with fatigue and injection site reactions being the most frequently reported events and only grade 1-2 events being related to the vaccine. Response was evaluated by RECIST 1.1, according to the investigator's assessment with 8 patients (67%) having objective response (CR: n = 2, PR: n = 6), of which 1 patients had response initiation before addition of the vaccine. Importantly the vaccine induced neoantigen specific T cells in all patients analyzed. Both CD4+ and CD8+ T cells were detected, with the majority of responses being CD4+ T cell mediated. Interestingly, we report a significant correlation between the PIONEER prediction score and induced immunogenicity. Furthermore, the breadth of the neoantigen recognition seemed to be important for the clinical effect of the vaccine as responders demonstrated T cell recognition of more epitopes within the vaccine compared to non-responders. We found, in our cohort, that the neo-antigen scores effectively separated responders and non-responders, as opposed to the TMB (by FDA guidelines). **Conclusions:** aPD-1 treatment combined with a peptide-based personalized neo-antigen-based vaccine was shown to be feasible and safe with promising signs of efficacy, warranting further study. Further, the neo-antigen selection method appeared crucial for designing an efficacious vaccine. Clinical trial information: NCT03715985. Research Sponsor: Innovation Fund Denmark; Evaxion Biotech.

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9552 **Poster Session**

Efficacy and safety of first-line (1L) nivolumab plus relatlimab (NIVO + RELA) versus NIVO plus ipilimumab (NIVO + IPI) in advanced melanoma: An indirect treatment comparison (ITC) using patient-level data (PLD).

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Background: NIVO + RELA and NIVO + IPI are approved as dual checkpoint inhibitor, 1L treatment options for patients (pts) with advanced melanoma based on results from the RELATIVITY-047 (NIVO + RELA vs NIVO; enrollment, 2018–2020) and CheckMate 067 (NIVO + IPI or NIVO vs IPI; enrollment, 2013–2014) trials, respectively. However, there is no head-to-head trial comparing the combinations; therefore, this ITC was conducted using PLD. **Methods:** To adjust for cross-trial imbalances in baseline characteristics, inverse probability of treatment weighting (IPTW) was used. Database locks were selected to best align follow-ups in RELATIVITY-047 (min., 21 mo; median, 25 mo) and CheckMate 067 (min., 28 mo; median, 29 mo). Efficacy and safety outcomes were selected based on data availability, including progression-free survival (PFS) per investigator, confirmed objective response rates (ORRs) per investigator, overall survival (OS), treatment-related adverse events (TRAEs), and TRAEs leading to discontinuation (DC). Efficacy was also evaluated in key subgroups. PFS and OS were compared for NIVO + RELA vs NIVO + IPI using Kaplan–Meier curves and hazard ratios (HRs); ORRs were compared using odds ratio (OR). As an internal validation of the ITC and matched assessments, the weighted NIVO cohorts from both trials were compared. **Results:** After IPTW, key baseline characteristics were balanced for NIVO + RELA (n = 340) and NIVO + IPI (n = 298). PFS, confirmed ORR, and OS after IPTW were similar between the treatments (table). Efficacy outcomes appeared to be similar between the treatments across subgroups, although trends favoring NIVO + IPI were observed for certain subgroups, such as pts with *BRAF* mutant disease or lactate dehydrogenase more than twice the upper limit of normal. Grade 3/4 TRAEs occurred in 23% and 61% of pts receiving NIVO + RELA and NIVO + IPI, respectively; any-grade TRAEs leading to DC occurred in 17% and 40% of pts. Efficacy outcomes were similar between the NIVO cohorts (table). **Conclusions:** In the absence of head-to-head trials, this ITC suggests that 1L treatment with NIVO + RELA may have comparable efficacy to, and better tolerability than, NIVO + IPI in pts with advanced melanoma. Similar outcomes between the NIVO cohorts support the ITC methodology. Results should be interpreted with caution given differences in study design and changes in treatment landscape over time. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (n = 340)	NIVO + IPI (n = 298)	HR/OR (95% CI)	NIVO RELATIVITY-047 (n = 338)	NIVO CheckMate 067 (n = 287)	HR/OR (95% CI)
Median PFS, mo (95% CI)	12.0 (8.2–15.8)	11.2 (8.4–17.5)	1.07 (0.87–1.31)	6.7 (4.6–10.2)	5.7 (3.1–8.9)	0.93 (0.76–1.13)
Confirmed ORR, %	48	50	0.93 (0.74–1.17)	40	39	1.03 (0.81–1.32)
Median OS, mo (95% CI)	NR (37.0–NR)	NR (31.9–NR)	0.94 (0.74–1.19)	36.8 (27.3–NR)	32.4 (25.8–NR)	0.95 (0.76–1.20)

NR, not reached.

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9553 **Poster Session**

Melanomas lacking HLA class I expression and response to checkpoint inhibitor.

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Background: The current paradigm of how checkpoint inhibitors (CPIs) mediate anti-tumor effects relies on αβ T cells as the effector cells. However, HLA class I allele expression loss is common in melanoma, and in some cases, both β2-microglobulin (β2m) alleles are silenced, which results in complete loss of HLA I expression. We reasoned that if CPI therapy requires αβ T cells as the effector cells, melanoma tumors with biallelic loss of β2m could not present antigen to αβ T cells and should never respond to CPI. **Methods:** We screened the 2754 melanoma patients (pts) whose tumors had been genotypically analyzed using MSK-IMPACT, a hybridization capture-based next-generation assay for targeted deep sequencing of all exons and selected introns of up to 505 genes, including β2m. We identified 13 pts who had been treated with CPI, were evaluable for response and progression-free survival, and whose pre-treatment melanoma was found to have biallelic loss of β2m. In 1 pt, only a post-treatment tumor was available for genetic testing for β2m loss but lack of β2m expression in a pre-treatment tumor was confirmed by immunohistochemistry (IHC). Pts were assessed for clinical responses using RECIST 1.1. We recorded best overall response, duration of response, and overall survival. When available, pre-treatment tumor tissue was assessed by IHC for β2m and HLA class I expression, and for lymphocytic infiltrates expressing CD3, CD4, CD8, and CD56. **Results:** Anti-tumor responses were observed in 3/13 patients (23%); 2 PRs, 1 metabolic CR lasting for 24, 9.4, and 6.4 months, respectively. Responses were to ipilimumab (ipi) (N=2) and ipi/nivolumab (N=1). One pt responding to ipi had progressed on pembrolizumab; the other 2 responders were treatment-naïve. One pt died 11.5 months after starting treatment; the other 2 pts remain alive 5.5 and 8.9 years after starting treatment. IHC confirmed the lack of cell surface expression of β2m and HLA class I in all 5 tumors available for IHC staining. IHC evaluations of lymphocyte infiltrates in tumors from 1 responder and 4 non-responders showed variable degrees of $CD3^+$ tumor infiltrating lymphocytes (TIL) with $CD4^+$ T cell predominance. Interestingly, the 1 responder had the least dense pretreatment TIL among the 5 cases. In all 5 tumors, $CD56^+$ lymphocytes, indicating NK cells, were rare-to-absent. **Conclusions:** Melanomas lacking HLA class I expression can respond to CPI therapy. Although all patients ultimately progressed, some responses were long-lived and 2 of 3 patients remain alive >5yrs. It seems unlikely that traditional $CD8^+$ T cells are mediating these responses but more work needs to be done to identify the effector cells in these cases. Research Sponsor: None.

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9554 **Poster Session**

Safety and preliminary efficacy of intrathecal (IT) and intravenous (IV) nivolumab (N) for patients (pts) with leptomeningeal disease (LMD).

Isabella Claudia Glitza, Ida John, Suzanne Phillips, Lauren See, Roland L. Bassett, Ruitao Lin, Michelle L. Rohlfs, Jessie Richard, Masood Iqbal, Tarin Hennegan, Ian E. McCutcheon, Sherise D. Ferguson, Golnaz Morad, Barbara Jane O'Brien, Sudhakar Tummala, Nandita Guha-Thakurta, Matthew Debnam, Hussein A. Tawbi, Elizabeth M. Burton, Michael A. Davies; MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; U T MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pts with LMD have a dismal prognosis, with median overall survival (OS) $<$ 3 months, no approved therapies and extremely limited clinical trial options. We previously reported initial safety findings from the dose escalation of an open label, single arm, single center phase I/IB trial (NCT03025256) for pts with metastatic melanoma (MM), in which IT/IV N were well tolerated, without any CNS-specific or unexpected toxicity. Here we report an update on safety, maximum tolerated dose (MTD), and dose expansion cohort (including 2 pts with NSCLC) and preliminary efficacy. **Methods:** Pts aged $\geq$18 with evidence of LMD by MRI and/or CSF cytology, ECOG PS $\leq$2 were treated with IT/IV N. Dexamethasone (dexa) $\leq$4mg/daily and concurrent BRAF/MEK inhibitor(i) therapy (tx) were allowed. For cycle 1, IT N was administered via ommaya reservoir on day (D)1. For subsequent cycles (every 14 days) pts received IT N on D1, followed by IV N 240 mg on D2. IT N doses evaluated were 5, 10, 20, and 50 mg. Blood and CSF were collected at multiple time points for translational research. The primary objectives were to determine safety and/or recommended dose/MTD of IT N given with IV N in pts with LMD and the safety of the MTD in an expansion cohort. OS was a secondary objective. Bayesian mTPI methodology was used to define the MTD. **Results:** 50 pts were treated: 17 in the dose escalation (2 at 5; 3 at 10; 6 at 20; 6 at 50 mg IT N), 8 in the initial expansion of 20mg, and 25 at the MTD 50 mg IT N. 48 pts had a diagnosis of MM, 2 NSCLC. Median age at LMD was 49 (19-74); 27 pts are male. All pts had radiographic evidence of LMD; 26 pts had positive baseline CSF cytology. 46 pts received prior systemic tx including checkpoint inhibitors (n = 42) and targeted tx (n = 34). 39 pts had prior CNS radiation (RT), including whole brain RT (n = 14). 18 pts used concurrent steroid, with a median dose of 2mg (0.9-4) dexa equivalent and 27 pts used concurrent targeted tx with BRAF/MEKi. The median number of IT N doses was 6 (1- 92). The combination regimen was well tolerated by all evaluable pts (n = 50), with 9 pts (18%) experiencing grade (gr) 3 AEs and no reported gr 4 or 5 toxicities. Rash (58%), nausea (44%), vomiting (34%), and dizziness (22%) were the most common AEs. Thirty pts (60%) experienced AEs after IT N administration, all gr 1/2 and 1 gr 3 (vasogenic edema). At a median follow-up of 4.6 months (mths) (0, 54.8 mths), median OS was 7.0 mths. OS was 66.6% at 3 mths, 53.1% at 6 mths and 34.8% at 12 mths. **Conclusions:** IT + IV nivo was safe and well-tolerated in MM pts with LMD, with no unexpected toxicities of the 50 mg MTD of IT N. OS rates at 6 and 12 mths are encouraging and support further evaluation of IT immunotherapy for LMD, including in other tumor types. Overall results also demonstrate the feasibility of prospective clinical trials in pts with LMD. Final presentation will also include immunological analysis of longitudinally collected CSF samples collected in the trial. Clinical trial information: NCT03025256. Research Sponsor: BMS; AMRF (Foundation): Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; U.S. National Institutes of Health; BMS.

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9557 **Poster Session**

High dose ipilimumab (Ipi) plus temozolomide (TMZ) after progression on standard or low dose Ipi in advanced melanoma.

Julie Williamson, Muhammad Zaki Hidayatullah Fadlullah, Magdalena Kovacsovics, Berit Gibson, Alyssa Erickson-Wayman, Debra Jamison, Daniel S. Sageser, Umang Swami, Joanne M. Jeter, Tawnya Lynn Bowles, Donald Maurice Cannon, Ben Haaland, Joyce Schroeder, Jordan P. McPherson, John Robert Hyngstrom, Aik-choon Tan, Siwen Hu-Lieskovan; Department of Internal Medicine, University of Utah, Salt Lake City, UT; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Huntsman Cancer Institute, Salt Lake City, UT; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Intermountain Medical Center, Murray, UT; University of Utah, Salt Lake City, UT; Huntsman Cancer Institute at the University of Utah, Salt LAKE Cty, UT

Background: Despite advancements in checkpoint inhibitor-based immunotherapy (IO), patients (pts) with advanced melanoma who have progressed on Ipi + nivolumab (Nivo) continue to have poor prognosis. Several studies support a dose-response activity of Ipi. One promising combination for these pts is Ipi 10mg/kg (Ipi10) + TMZ. TMZ depletes regulatory T cells and suppresses their function, and it may enhance the antitumor activity of Ipi. We studied outcomes of pts with advanced melanoma treated with Ipi10+TMZ in the IO refractory/resistant setting, using a cohort of similar pts treated with Ipi3+TMZ as comparison. **Methods:** Clinical data of pts with IO refractory melanoma treated with Ipi+TMZ was collected retrospectively following IRB approval. Molecular profiling by WES and RNAseq of tumors harvested throughout one responder's treatment were analyzed: the primary skin lesion (P1), a liver metastasis (M2) 2 days after low-dose Ipi1+Nivo, and a soft tissue metastasis (M3) after Ipi10+TMZ. **Results:** Overall 12 pts met eligibility: 6 received Ipi10 and 6 received Ipi3. All pts in Ipi10 cohort had progressed on prior Ipi+Nivo. Two pts (33% ORR) with CNS involvement demonstrated extraordinary near complete responses to Ipi10+TMZ despite progressing on prior therapies, including regular or low dose Ipi+Nivo. With a median follow up of 119 days, pts treated with Ipi10+TMZ had statistically significant longer median progression free survival (PFS) of 144.5 days (range 27–219) vs 44 (26–75) for Ipi3+TMZ, $p = 0.04$. There is a trend for longer median PFS for pts who had > 1 cycle of treatment, and for those who had progressed on prior Ipi+Nivo. There is a trend for longer median overall survival (OS) of 154.5 days (27–537) with Ipi10 vs 89.5 (26–548) for Ipi3 +TMZ. In those previously exposed to Ipi3+Nivo, median OS in the Ipi10+TMZ group was 154.5 days (27–537) vs 39 (26–55) in Ipi3+TMZ group. WES of one responder's tumors revealed only 12 shared somatic mutations among P1, M2 and M3, including BRAF V600E, suggesting common lineage but significant clonal evolution. Genes involved in several important immune response pathways were mutated in M2 and M3 but not in P1. RNAseq showed enrichment of inflammatory signatures, including interferon responses in both M2 and M3 compared to P1, and downregulated negative immune regulators such as Wnt and TGFb signaling. M2 is a responding liver lesion to prior Ipi1+Nivo but disease progressed to bones and brain that subsequently responded to Ipi10+TMZ. **Conclusions:** Ipi10+TMZ demonstrated efficacy including dramatic responses in pts with advanced melanoma refractory to standard or low doses of Ipi + anti-PD1, even with CNS metastases. Molecular data suggest a potential threshold of Ipi dose for activation of sufficient anti-tumor immune response, and higher dose Ipi is required for some pts. Research Sponsor: None.

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9558 **Poster Session**

The impact of emotional distress on pathologic response and survival after neoadjuvant combination immune checkpoint blockade (ICB) in high-risk stage III melanoma.

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Background: Neoadjuvant ICB has been shown to induce high pathologic response rates in high-risk stage III melanoma, outperforming adjuvant ICB with respect to survival benefit. Biomarkers that have been shown to predict ICB efficacy, including the interferon-gamma (IFN-γ) signature and tumor mutational burden (TMB), do not completely explain why some patients (pts) fail to benefit from neoadjuvant ICB. Emerging evidence in preclinical and clinical studies suggests that emotional distress (ED) negatively affects tumor progression and anti-tumor immune responses, mediated by β-adrenergic and glucocorticoid signaling. Here, we investigate the association between ED prior to neoadjuvant ICB and pathologic response and survival in pts with stage III melanoma treated in the PRADO trial. **Methods:** PRADO tested neoadjuvant ipilimumab + nivolumab followed by a response-directed surgical and adjuvant treatment regimen in stage III melanoma pts. The European Organization for Research and Treatment of Cancer (EORTC) scale for emotional functioning was used to identify pts with ED, based on established clinically relevant thresholds. Association between ED and pathologic response or survival was assessed using multivariable logistic or Cox regression analysis. Potential effects of ED on the tumor and its microenvironment were examined in baseline tumor biopsies using RNA sequencing. **Results:** Pts who completed the baseline EORTC questionnaire were included and defined as pts with ED (n = 28) or without ED (n = 60). Baseline characteristics, IFN-γ signature expression and TMB were comparable. Pts with ED showed a trend towards achieving less major pathologic responses (MPR; ≤10% viable tumor) compared to pts without ED (46% vs 65%, p = 0.099). Multivariable analysis showed a significant association between ED and MPR (OR 0.20, p = 0.043) when adjusted for age, sex, IFN-γ signature (OR 9.36, p = 0.002) and TMB (OR 13.21, p = 0.003). Pts with ED also had a significantly lower relapse-free survival (RFS) compared to pts without ED (2-year RFS 74% vs 91%, p = 0.011), and ED at baseline remained associated with relapse in multivariable regression (HR 3.81, p = 0.034) when adjusting for IFN-γ signature (OR 0.34, p = 0.109) and TMB (OR 1.02, p = 0.972). Analyses investigating the relation between ED with β-adrenergic and glucocorticoid signaling and factors representing anti-tumor immune responses are ongoing and will be presented at ASCO. **Conclusions:** Emotional distress was identified as baseline marker associated with impaired clinical outcomes after neoadjuvant combination ICB in pts with high-risk stage III melanoma. This data warrants further investigation in independent cohorts and into the potential effect of pharmacological and psychosocial interventions, e.g. adrenergic receptor blockade, on the anti-tumor immune response and patient outcomes. Clinical trial information: NCT02977052. Research Sponsor: BMS.

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9559 **Poster Session**

A phase 2 study of alrizomadlin (APG-115) in combination with pembrolizumab in patients with unresectable or metastatic cutaneous melanoma that has failed immuno-oncologic (IO) drugs.

Montaser F. Shaheen, Jennifer Margaret Segar, Bartosz Chmielowski, Joseph J. Drabick, Meredith McKean, James A. Reeves, Christos Stelios Karapetis, Marlana M. Orloff, Anthony W. Tolcher, J. Thaddeus Thaddeus Beck, Brian Gastman, Asit De, Ben Paudyal, Robert E Winkler, Mingyu Li, Mohammad Ahmad, Dajun Yang, Yifan Zhai; University of Texas Health Science Ctr, San Antonio, TX; The University of Arizona Cancer Center, Tucson, AZ; Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA; Penn State Hershey Medical Center Cancer Institute, Hershey, PA; Sarah Cannon Research Institute at Tennessee Oncology, PLLC, Nashville, TN; Florida Cancer Specialists-South/Sarah Cannon Research Institute, Fort Myers, FL; Flinders Medical Centre, Bedford Park, SA, Australia; Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; NEXT Oncology, San Antonio, TX; Highlands Oncology, Springdale, AR; Cleveland Clinic, Cleveland, OH; Ascentage Pharma Group Inc., Rockville, MD; Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China; Ascentage Pharma Group Inc., Rockville, MD

Background: Alrizomadlin is a novel, orally active small-molecule MDM2 inhibitor that activates p53-mediated apoptosis in tumor cells, also functions as a host immunomodulator, and may restore antitumor activity in patients with cancer that has progressed on PD-1/PD-L1 inhibitors. Alrizomadlin is currently being investigated for treatment of patients with unresectable or metastatic cutaneous melanoma that progressed on prior immunotherapy. **Methods:** This multicenter clinical trial was conducted in the United States and Australia in patients with unresectable or metastatic cutaneous melanoma that had progressed on PD-1/PD-L1 immunotherapy. Eligible patients had an ECOG performance status of 0-2. Alrizomadlin 150 mg was administered orally every other day for 2 consecutive weeks, with 1 week off, and pembrolizumab 200 mg intravenously for 30 minutes on Day 1 of a 21-day cycle. **Results:** As of December 12, 2022, preliminary and interim results are reported for 31 patients with cutaneous melanoma, of whom 21 were male and 10 female, with a median (range) age of 65 (27-84) years. Treatment-related adverse events (TRAE) of any grade ($>$ 10%) for either alrizomadlin or pembrolizumab were reported in 30/31 (96.8%) patients. These AEs included nausea (71%), vomiting (38.7%), fatigue (35.5%), thrombocytopenia (32.3%), diarrhea (25.8%), neutropenia (19.4%), decreased appetite (16.1%), and decreased leukocyte count (12.9%). A total of 4/31 (12.9%) patients reported treatment-related serious AEs, including anemia, thrombocytopenia, deep vein thrombosis, joint effusion, pulmonary embolism, and vomiting. In 26 efficacy-evaluable patients, the confirmed overall response rate (ORR; partial response [PR] + complete response [CR]) was 23.1%, including 2 patients reporting CRs and 4 reporting PRs based on RECIST v.1.1. The initial analysis indicated that the ORR observed in patients whose disease had failed IO treatment was primarily due to alrizomadlin combined with pembrolizumab, not the delayed effect of prior immunotherapy. **Conclusions:** Alrizomadlin combined with pembrolizumab is well tolerated and demonstrates clinical efficacy in these patients with highly refractory unresectable or metastatic cutaneous melanoma that had progressed on PD-1/PD-L1 immunotherapy. Internal study identifier: APG-115-US002. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong) and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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9560 **Poster Session**

Machine learning (ML)-based quantification of tumor-infiltrating lymphocytes (TIL) and clinical outcomes of patients with melanoma treated with immune-checkpoint inhibitors (ICI).

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Background: TIL quantification has shown promising prognostic and predictive impact in various tumors treated with ICI. More recently, TIL therapy has become an emerging treatment agent for ICI-refractory melanoma. In this work, we studied the effect of intrinsic TILs on clinical outcomes of patients with melanoma treated with ICI and quantified its utility as a biomarker in combination with tumor mutational burden (TMB). **Methods:** We applied a previously developed ML model to process digital whole-slide images of hematoxylin and eosin slides to quantify TIL density (TIL/mm2) in 182 metastatic melanoma samples treated with ICI at the Dana-Farber Cancer Institute. All samples underwent next-generation targeted-panel sequencing and had available TMB data (mutations/megabase). Overall survival (OS) was calculated from the data of ICI initiation to the date of death. TTF was calculated from the data of ICI initiation to the date of next line treatment or death. Alive patients were censored at the date of last follow-up. Multivariable cox regression was used to estimate adjusted hazard ratios (adj-HR) and p-values (adj-p), with TMB, prior lines of treatment and regimen type (single vs. combination ICI) used as covariates. TMB-high (TMB-H) group was defined as samples with TMB≥10. TIL-high (TIL-H) group was defined as samples with TIL density higher than the median. **Results:** Of 182 patients, 60% (110/182) were male and the median age at ICI start was 65.5 years. 63% (115/182) of patients received single-agent ICI (anti-PD1 or anti-CTLA4). Of 182 tumor specimens assessed for TILs, 47 (25.8%) were obtained from the primary site. There was no difference in TIL density (medians 583 vs. 817 TILs/mm2, p=0.57; 709 TIL/mm2 for full cohort) or TMB (medians 11.4 vs 12.2 mutations/megabase) between primary and metastatic samples, respectively. Moreover, there was no correlation between TIL density and TMB (pearson's correlation coefficient = 0.92, p=1) across all samples. Compared to patients in the TIL-low (TIL-L) category, patients in TIL-H had significantly longer median TTF (33.9 [15.9-NR] versus 13.0 [7.8-18.6] months, adj-HR: 0.53 (95% CI: 0.36-0.78); adj-P=0.0012), while there was no difference in OS (P=0.57). In fact, patients in the TMB-H/TIL-H group had the longest TTF, followed by TMB-H/TIL-L, TMB-L/TIL-H then TMB-L/TIL-L (table). **Conclusions:** Our results support the potential use of ML-based TIL scoring as a novel and independent biomarker to predict time to failure on ICI. There is ongoing effort to validate our findings in an external dataset. Research Sponsor: None.

Group	Median OS (months)	Median TTF (months)
TMB-H/TIL-H	74.0 [45.7 – NR] months	49.0 [26.6 – NR] months
TMB-H/TIL-L	NR [43.2 – NR] months	23.3 [14.4 – NR] months
TMB-L/TIL-H	50.5 [24.5 – NR] months	15.5 [8.1 – 33.9] months
TMB-L/TIL-L	29.0 [18.1 – NR] months	6.4 [5.0 – 12.9] months

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9561 **Poster Session**

Correlation of DNA methylation signatures with response to immune checkpoint inhibitors in metastatic melanoma.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of metastatic melanoma with objective response rates of 40-58%. However, reliable biomarkers to predict treatment response are lacking. Tumor tissue methylation profiles were recently proposed to have predictive value in various solid organ tumor entities. **Methods:** Patients with metastatic melanoma, American Joint Committee on Cancer (AJCC; 8th Edition) stage IV, receiving first-line ICI-based therapy, were retrospectively identified and formalin-fixed paraffin-embedded tumor tissue samples (FFPE) prior to ICI therapy were retrieved. We analyzed DNA methylation profiles of $>$ 850.000 CpG sites in tumor specimens by Infinium MethylationEPIC microarrays. DNA methylation profiles were then correlated with radiological response (iRECIST). **Results:** 71 patients with metastatic melanoma (44 (62.0%) male, 27 (38.0%) female) were investigated; median progression free survival (PFS) was 8.5 months (range: 0 – 104.1 months) and median overall survival (OS) was 30.6 months (range: 0 – 104.1 months), respectively. 29 (40.8%) patients achieved an objective response to ICIs. Microarray analyses revealed a methylation signature including mainly hypomethylation, corresponding to the response to ICIs. Based on the 500 mostly differentially methylated genes, a total of 3 clusters were identified with the majority of responders being in cluster 2 (12/12) and 3 (12/22). The predictive performance of the methylation signature was high with 80% sensitivity, 81% specificity, and an AUC of 0.853. **Conclusions:** Our findings suggest that tumor DNA methylation profiling may be useful to predict response to ICIs in patients with metastatic melanoma. Research Sponsor: Christian Doppler Research Association and the Austrian Federal Ministry for Digital and Economic Affairs, the National Foundation for Research, Technology and Development.

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9562 **Poster Session**

Association of ultra-sensitive ctDNA assay to identify actionable variants and response to immune checkpoint inhibitor (ICI) therapy in metastatic melanoma.

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Background: Detection of molecular residual disease (MRD) via circulating tumor DNA (ctDNA) can identify therapeutic response/resistance months in advance of imaging, and monitoring clinically actionable variant dynamics in ctDNA may be important for guiding treatment. Despite this, adoption has been slow due to the reduced sensitivity and reproducibility of current approaches. Here, we profile melanoma patients receiving ICI over several years using an ultra-sensitive, tumor-informed ctDNA platform, and correlate the findings with clinical outcome. **Methods:** Over 150 plasma samples from 23 advanced melanoma patients (stage IV) were collected during ICI treatment (up to 40 months) and profiled with NeXT Personal, a tumor-informed ctDNA assay that leverages whole-genome sequencing of tumor/normal samples to generate personalized liquid biopsy panels. Each bespoke panel consists of up to 1,800 selected variants which enable sensitive MRD detection, and a fixed set of 2,100 known clinically actionable and resistance loci for detection of variants emerging under therapeutic pressure. MRD signal and variant dynamics were then correlated with RECIST assessments and outcome. **Results:** In this cohort, ctDNA was detected across a broad dynamic range (2.3-100,000 PPM; median limit of detection = 1.97 PPM) with 37% of detections occurring below 100 PPM. Baseline ctDNA was detected in 94% (17/18) of patients, and was significantly correlated with S100B and metastatic burden (Spearman's rho, 0.73 and 0.5; p, 0.0002 and 0.025). The mutation-rate normalized count of melanoma-specific driver genes detected at baseline predicted reduced overall survival (OS) ($p = 0.03$). 94% (17/18) of ctDNA+ patients displayed dynamic variant allele frequency (VAF) shifts, impacting 149 loci across 37 ICI-related genes including BRAF, CDKN2A, KIT, MAP2K1, and NRAS. Delta ctDNA from baseline to the first on-treatment time point correlated with PFS (log rank $p = 0.004$). Treatment elicited greater than 3-fold reduction in average PPM, and the magnitude was significantly correlated with progression ($p = 0.0005$). VAF increases in known ICI-related genes (JAK1, ALK, etc) predicted shortened OS ($p = 0.007$) and fewer variants in genes conferring sensitivity to (NRAS, BRAF, etc) ICI were detected on-treatment in progressing patients ($p = 0.025$). **Conclusions:** We tracked both tumor-informed MRD and tumor-agnostic evolution of ICI related variants over the course of treatment using a single liquid biopsy platform. We achieved ultra-sensitive ctDNA detection down to 2.3 PPM and dynamics in ctDNA signals were predictive of clinical outcome. Furthermore, we demonstrated that ctDNA measurements and VAF dynamics of clinically actionable and resistance variants correlated with response as well as resistance to ICI. Research Sponsor: University Medical Center Hamburg-Eppendorf (UKE); Hiege Stiftung - German Skin Cancer Foundation.

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9563 **Poster Session**

Interim analysis of a phase II study of nivolumab/ipilimumab plus cabozantinib in patients with unresectable advanced melanoma.

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Background: Nivolumab/ipilimumab (Nivo/Ipi) is a standard therapy in patients with unresectable stage III/IV melanoma, demonstrating an objective response rate (ORR) of 58% and 12-month progression free survival (PFS) rate of 49% [Wolchok J, NEJM 2017]. c-MET/VEGFR2 inhibition with cabozantinib (Cabo) has modest clinical activity in melanoma and can augment antitumor immunity by increasing CD8+ Tcell and macrophage tumor infiltration, decreasing intratumoral regulatory Tcell levels, and increasing tumor cell MHC antigen presentation. Nivo/Ipi plus Cabo showed clinical activity and acceptable toxicity profile in GU malignancies [Apolo AB, JCO 2020]. We performed a study of Nivo/Ipi plus Cabo in advanced melanoma patients aimed at improving efficacy. **Methods:** We conducted a multicenter phase II study of induction Nivo 3mg/kg IV and Ipi 1mg/kg IV and Cabo 40mg PO daily every 3 weeks for 4 cycles, followed by Nivo 480mg IV plus Cabo 40mg PO daily every 4 weeks for up to 2 years, until disease progression or unacceptable toxicity/patient withdrawal. Patients with unresectable stage III/IV melanoma and no prior anti-PD-1 or CTLA-4 exposure (unless in adjuvant setting $>$ 6 months since last dose) were included. Uveal melanoma excluded. Primary endpoint was 12-month PFS rate. Secondary endpoints included ORR, overall survival (OS), and adverse events (AEs). Interim analysis was preplanned after first 14 subjects were evaluated in a Simon 2 stage design (goal $>$8 subjects 12-month progression free). **Results:** As of 1/2023, 14 subjects were enrolled across three cancer centers within the Georgetown-Lombardi Comprehensive Cancer Center Consortium. Median age 66.5 years, all stage IV disease, 10 with cutaneous primary site, 5 with elevated LDH, and 6 with BRAF V600 mutant tumor. Median follow up was 10.6 mos. 12-month PFS rate was 30% (3/10 evaluable subjects); 3 subjects pending PFS evaluation; median PFS 10.3 mos. ORR was 46% (6/13 evaluable subjects) with 2 CR, 4 PR, and 1 SD. Responders had cutaneous (5) or unknown (1) primary sites. 9 patients were alive at last follow up. 12-month OS rate was 67% (6/9 evaluable subjects). Reasons for treatment discontinuation included AEs (4), patient withdrawal (1), and disease progression (6). 3 subjects remain on study drug(s). Treatment related AEs (TRAEs) were observed in 13 subjects; 9 experienced a grade 3-4 TRAE (most frequent were elevated AST/ALT 29% and hypokalemia 14%). Most frequent grade 2 TRAEs were diarrhea (35%) and palmar-planter-erythrodysesthesia (29%). No treatment related deaths occurred. **Conclusions:** Clinical activity was observed with Nivo/Ipi plus Cabo in advanced melanoma but did not meet the predefined threshold to advance to the second stage of enrollment. TRAE profile was similar to prior reports. Biomarker analyses are planned to identify patient profiles associated with particular benefit from this regimen. Clinical trial information: NCT04091750. Research Sponsor: Exelixis.

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9564 **Poster Session**

Analysis of overall survival (OS) and progression-free survival (PFS) in the phase 1b clinical trial of anti–PD-1 ab (toripalimab) plus intrahepatic injection of orienX010 in stage IV melanoma with liver metastases.

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Background: Advanced melanoma with liver metastasis has a lower response rate and survival even in immunotherapy era which might because of its immunosuppressive tumor microenvironment. CPI combined with TVEC had showed a remarkable in cutaneous melanoma. The initial results of the phase 1b trial, systemic toripalimab (anti-programmed cell death-1 antibody) combined with Intratumoral injection of liver with OrienX010 - a HSV-1-derived oncolytic virotherapy with expression of GM-CSF in liver metastasis patients without extra-hepatic injectable lesions had shown its efficacy. Here we present the PFS and overall survival (OS) outcomes. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extra-hepatic metastasis; the ocular melanoma and brain metastasis were excluded. Pts received intravenous toripalimab Q2W combined with ultrasound guided intratumoral injection of OrienX010 Q2W (8×10^7 pfu/ml, 10ml per injection) until intolerance or disease progression per iRECIST criteria. Liver biopsy would be performed at baseline and first tumor evaluation (8-12weeks). The primary endpoint was toxicity; secondary endpoints included ORR, disease control rate (DCR), PFS and OS. Clinical trial information: NCT04206358. **Results:** From Jul 2019 to Feb 2023, 30 pts enrolled. 60.0% pts primary from mucosal,; 73.3% got extra-hepatic metastasis; median size of injected lesions: 24mm(10-94mm); median number of liver metastasis: 7(1-10); median number of injection: 10 (3-36). Among these pts, 29 pts could be evaluated for efficacy. The median PFS was 7.0months (95%CI: 4.7-9.3 months) and the median OS was not reached. The 3-year OS rates 51.5%. The global ORR by investigator was 20.7% (6/29), DCR 48.3% (14/29); the response rate was 31.0%(9/29) for injected lesions, 30.0%(6/20) for non-injected lesions in liver, and 27.8% (5/18) for extra-hepatic metastases. For pts (21.7%(2 PR and 3 SD)) with no melanoma cells residual by immunohistochemistry in biopsies the median PFS was 14.0 months (95%CI: 3.7-24.4 months), and it was much longer than that of other pts which was 4.1 months (95%CI: 1.4-6.8 months). The median OS of the pts with no melanoma cells was 19.7 months (95%CI: 7.5-31.9 months). Most adverse events (AE) were grade 1-2 and manageable. The grade 3-4 treatment-related AE included elevated transaminase (3 [10.0%]), nausea (1 [3.3%]), pulmonary embolism (1 [3.3%]) and vomiting (1 [3.3%]). No treatment-related deaths occurred. **Conclusions:** Systemic toripalimab combined with intrahepatic OrienX010 injection has shown remarkable long PFS, OS and ORR in melanoma pts with liver metastases with manageable toxicity. Clinical trial information: NCT04206358. Research Sponsor: None.

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9565 **Poster Session**

Expression of lymphoid structure-associated cytokine/chemokine gene transcripts in tumor and protein in serum: Outcomes for patients with melanoma.

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Background: Proinflammatory chemokines/cytokines support development and maturation of tertiary lymphoid structures (TLS) within the tumor immune microenvironment (TIME). In the current study, we sought to investigate the prognostic value of TLS-associated chemokine/cytokine (TLS-kine) expression levels in melanoma patients (MEL PTs) by performing serum protein and tissue transcriptomic analyses, and to then correlate these data with PT tumor clinicopathological and TIME characteristics. **Methods:** Levels of TLS-kines in PT sera were quantitated using a custom Luminex Multiplex Assay. The Cancer Genomic Atlas MEL cohort (TCGA-SKCM) and a Moffitt MEL cohort were used for tissue transcriptomic analyses. Associations between target analytes and survival outcomes, clinicopathological variables, and correlations between TLS-kines were statistically analyzed. **Results:** Serum of 95 PTs with MEL were evaluated; 48 (50%) female, median age of 63, IQR 51-70 years. Serum levels of APRIL/TNFSF13 were positively correlated with levels of both CXCL10 and CXCL13. Tumors with brisk/non-brisk tumor-infiltrating lymphocytes (TIL) vs. absence of TIL exhibited significantly higher levels of APRIL/TNFSF13 ($p = 0.01$), CCL19 ($p = 0.01$) and CXCL13 ($p = 0.01$). In multivariate analyses, high levels of serum APRIL/TNFSF13 were associated with improved event-free survival after adjusting for age and stage (HR = 0.64, 95% CI 0.43-0.95; $p = 0.03$). High expression of *APRIL/TNFSF13* transcripts was significantly associated with improved OS in TCGA-SKCM[n = 448](HR = 0.69, 95% CI 0.52-0.93; $p = 0.01$) and in Moffitt MEL PTs [n = 134] (HR = 0.51, 95% CI: 0.32-0.82; $p = 0.006$). Further incorporation of *CXCL10* and *CXCL13* transcript levels in a 3-gene index revealed that high *APRIL/CXCL10/CXCL13* expression was associated with improved OS in the TCGA SKCM cohort (HR = 0.42, 95% CI 0.19-0.94; $p = 0.035$). High coordinate expression of the *TNFSF13/CXCL10/CXCL13* transcripts in MEL was correlated with an increased presence of naïve B cells, plasma B cells, $CD8^+$ T cells, and M1 macrophages and decreased levels of M2 macrophages and mast cells as well as a reduced neural network gene signature. **Conclusions:** Serum protein and tumor transcript levels of APRIL/TNFSF13 are associated with improved survival outcomes. PTs exhibiting high coordinate expression of *APRIL/CXCL10/CXCL13* transcripts in their tumors displayed superior OS. MEL differentially expressed genes positively associated with high coordinate *APRIL/CXCL10/CXCL13* expression were linked to tumor infiltration by a diverse array of proinflammatory immune cell types. Further investigation of TLS-kine expression profiles related to clinical outcomes is warranted. Research Sponsor: Melanoma Center Internal Funding at the University of Pittsburgh Medical Center, NIH P01 CA234212-01A1 (Walter Storkus); Conquer Cancer Foundation of the American Society of Clinical Oncology.

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9566 **Poster Session**

Exploring the clinical significance of specific immune-related adverse events (irAE) in patients with melanoma undergoing immune checkpoint inhibitor (ICI) therapy.

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Background: Several studies have demonstrated that patients who experience irAE as a result of ICI treatment, exhibit significantly improved outcomes compared to patients without toxicity. However, data regarding the impact of specific irAE is currently lacking. **Methods:** This is a real world single-site cohort of advanced melanoma patients who were treated with ICI as first line between 2014 and 2020. This study explores the effects of specific irAE on treatment efficacy. **Results:** Three hundred and ninety-five (395) patients were treated with either monotherapy anti PD-1 (65.4%), combination ICI (24.3%), or anti CTLA-4 (10.3%). Median age was 68 years (12-99y), and 57% were male. The median follow up was 24.5m. Any-grade irAEs were seen in 72% (n = 299), and 26% experienced high-grade irAE (n = 104). The most frequent irAE were dermatologic (n = 110, 27.8%), vitiligo (n = 48, 12.1%), rheumatologic (n = 68, 17.2%), gastro-intestinal (n = 66, 16.7%), and endocrine (n = 61, 15.4%). The development of irAE was associated with a significantly longer median PFS (19.3m vs 4.5m; HR 0.46, $p < 0.001$) and median OS (55m vs 16.9m; HR 0.44, $p < 0.001$). Specific irAE that were significantly associated with survival benefic were rheumatologic (HR 0.34 for PFS, $p < 0.001$; HR 0.38 for OS, $p < 0.001$), dermatologic (HR 0.58 for PFS, $p < 0.001$; HR 0.54 for OS, $p = 0.001$), vitiligo (HR 0.30 for PFS, $p < 0.001$; HR 0.29 for OS, $p < 0.001$) and endocrine (HR 0.6 for PFS, $p = 0.01$; HR 0.52 for OS, $p < 0.001$). After adjustment for ECOG performance status, LDH level, type of ICI protocol and M-substage - the rheumatologic, dermatologic and vitiligo irAE remained significant on multivariate analysis for both PFS and OS. **Conclusions:** The development of rheumatologic, vitiligo and other dermatologic irAE during ICI treatment, is correlated with a noteworthy survival advantage. These irAE may reflect a hyper-activated immune response and thus can serve as meaningful clinical biomarkers.
Research Sponsor: None.

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9567 **Poster Session**

Transforming growth factor-b1 and soluble co-inhibitory immune checkpoints as putative drivers of immune suppression in advanced basal cell carcinoma.

Bernardo Leon Rapoport, Ronald Anderson, Nonkululeko Malinga, Helen C. Steel, Pieter Meyer, Teresa Smit, Mahlatse Kgokolo; Department of Immunology, Faculty of Health Science, University of Pretoria, Pretoria, South Africa; University of Pretoria, City of Tshwane, South Africa; Department of Dermatology, Faculty of Health Sciences, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa; University of Pretoria, Department of Immunology, Pretoria, South Africa; Department of Immunology, School of Medicine, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa; The Medical Oncology Centre of Rosebank, Johannesburg, South Africa

Background: BCC rarely metastasizes and the mortality rate is low; however, the disease is associated with substantial morbidity. Transforming growth factor-b1 (TGF-b1) is a key player in cell proliferation, differentiation, apoptosis, and immune regulation. TGF-b1 is associated with immunosuppression and resistance to immunotherapeutic drugs. Immune checkpoint proteins (ICMs) maintain self-tolerance and modulate the immune responses of effector cells. The current study compared the levels and possible associations between systemic soluble ICMs (sICMs) and a group of humoral modulators of immune suppressor cells in a cohort of patients with advanced basal cell carcinoma (BCC, n = 40) and a group of healthy control subjects (n = 20). **Methods:** We measured sICMs and immunosuppressive humoral modulators by using multiplex bead array or ELISA procedures, with plasma as the matrix. The sICMs comprised seven co-inhibitory (CTLA-4, BTLA, LAG-3, PD-1, PDL-1, PDL-2, and TIM-3) and eight co-stimulatory (CD27, CD28, CD40, CD80, CD86, GITR, GITRL, and ICOS) proteins, as well as the two dual-active sICPs, HVEM and TLR2. The seven humoral modulators of immunosuppressor cells included arginase 1, fibroblast activation protein (FAP), RANTES (Regulated upon Activation Normal T Cell Expressed and Presumably Secreted) also known as CCL5, interleukin-10 (IL-10), TGF-b1, and the M2-type macrophage biomarkers, soluble CD163 (sCD163) and sCD206. Ethics approval was granted by The Research Ethics Committee, Faculty of Health Sciences, University of Pretoria (Ethics Committee Approval Numbers 356/2020. **Results:** The plasma levels of six co-inhibitory sICPs, sCTLA-4, sLAG-3, sPD-1, sPD-L1, and sTIM-3 and sPD-L2 were significantly elevated in the cohort of BCC patients ($p < 0.001$-$p < 0.00001$), while that of sBTLA was significantly decreased ($p < 0.006$). Of the co-stimulatory sICPs, sCD27 was significantly increased ($p < 0.0002$) in the cohort of BCC patients, with the levels of the others essentially comparable with those of the control patients; of the dual active sICPs, sHVEM, sTLR2 was significantly elevated ($p < 0.00001$) and TLR2 comparable with the control group. Although the plasma levels of the seven modulators of immune suppressor function were not significantly different between the BCC and control groups, correlation heat maps revealed selective, strong associations of TGF-b1 with seven co-stimulatory (z = 0.618468-0.768131) and 4 co-inhibitory (z = 0.674040-0.808365) sICPs, as well as with sTLR2 (z = 0.696431). **Conclusions:** Notwithstanding the association of BCC with selective elevations in the levels of a large group of co-inhibitory sICPs, our novel findings also imply the probable involvement of TGF-b1 in driving immunosuppression in this malignancy, possibly via activation of regulatory T cells. Research Sponsor: Department of Immunology, University of Pretoria.

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9569 **Poster Session**

De-correlating immune checkpoint inhibitor toxicity and response in melanoma via the microbiome.

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Background: Immune-checkpoint inhibitor (ICI) immunotherapy increases survival in patients with melanoma. Yet only half of the patients respond, and 10-40% of patients experience immune-related adverse events (irAEs). Previous studies have found a correlation between the development of an irAE and treatment response. Modifying the gut microbiome could positively affect response to ICIs and reduce toxicities. We sought to determine if the microbiome at the onset of treatment, during an irAE, and at 12 weeks, can predict the response or toxicity during ICI treatment for metastatic melanoma. **Methods:** Melanoma patients (pts) $>$ 18 yo treated with ICI enrolled in a prospective observational cohort study at The Ohio State University Comprehensive Cancer Center Skin Cancer Clinic. Excluded were patients on corticosteroids at the start of ICI cycle 1, except for adrenal physiologic replacement. Stools were collected at baseline, within 2 days of an adverse event assessed by physician chart review using CTCAE (Common Terminology Criteria for Adverse Events) v5.0, and at 12 weeks. Response (ORR) to ICIs was assessed by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) q12 weeks and progression-free survival recorded. Metagenomic whole-genome shotgun sequencing was performed on an IIlumina NovaSeq 6000 and classified using HUMAnN3. The effect of microbe relative abundances on irAEs was modeled by logistic regression with the R package glmm. **Results:** Of the 88 patients enrolled, 48 had metastatic disease with 32 assessable for response. ORR at 12 weeks was 28% (1 CR, 8 PR, 17 SD, and 6 PD) and 24 patients showed PFS at 12 months. Grade $>$ 2 irAEs were observed in 11/48 pts. Abundance of *Bacteroides dorei* (False Discovery Rate Corrected p-value = 9.5E-07) and *Blautia species CAG:257* (padj = 0.001) were enriched in responders, *Prevotella Stercorea* (padj = 1.1E-07) and a phage with a predicted target of *Salmonella* (padj = 8.3E-09) in non-responders. Responders with an irAE had enrichment of *Bacteroides plebeius* (padj = 4.2E-13) and *Bacteroides coprophilus* (padj = 0.0002) whereas responders without irAE had enrichment of *Eubacterium siraeum* (padj = 7.2E-05). **Conclusions:** Longitudinal and event-driven biospecimen collection in patients treated with ICIs showed several bacteria and viruses but no fungi associated with response, with and without the development of an irAE. The abundance of the two high-taxonomic rank microbe groups is significantly associated with irAEs. The association with the *Bacteroides* Genus is consistent with previous studies and is associated with response to ICIs. A microbiome abundant in *Bacteroides* and lacking *Prevotella* is associated with response to ICI. An abundance of *Bacteroides* could be a biomarker for irAEs, and an abundance of *Eubacterium*, a biomarker for response without irAEs. Future analyses are necessary to assign causal roles for microbe biomarkers with specific irAEs. Clinical trial information: NCT05102773. Research Sponsor: Pelotonia.

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9570 **Poster Session**

Overall survival after the introduction of adjuvant treatment in stage III melanoma: A nationwide registry based study.

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Background: Adjuvant treatments with PD-1 and BRAF+MEK inhibitors significantly prolong recurrence-free survival in stage III cutaneous melanoma. However, the effect on overall survival is still unclear. After the approval of adjuvant treatments with PD-1 inhibitors and BRAF+MEK inhibitors, based on recurrence-free survival data, these treatments have been widely implemented. However, there are significant side effects and costs of the treatment, and the overall survival effect remains a highly anticipated outcome. **Methods:** Clinical and histopathological parameters were obtained from the Swedish Melanoma Registry that covers nearly all (99%) primary cutaneous melanomas diagnosed. Information on deaths was received from the Cause of Death Registry, a virtually complete register of all deaths in Sweden. Patients diagnosed with stage III melanoma between 2016 and 2020 were included and divided depending on if they were diagnosed before or from July 2018, the timepoint when adjuvant treatment was introduced in Sweden (designated as pre- and post-cohorts). In Sweden, approved treatments are freely available for all residents and there is a high-adherence to national treatment guidelines. Data was retrieved for the age and sex of the patients, the site, histopathological subtype, Breslow thickness and ulceration of the primary melanoma, type of locoregional spread and numbers of affected lymph nodes. Patients were followed until the end of 2021. Melanoma-specific and overall survival were calculated using the Kaplan-Meier method and Cox regression analyses. **Results:** There were 1371 patients diagnosed with stage III melanoma in Sweden in 2016-2020. The median time of follow-up in the pre-cohort was 57 months (range 42-72 months) and in the post-cohort 27 months (range 12-42 months). The 2-year overall survival rates, comparing the 634 patients in the pre-cohort and the 737 in the post-cohort, were 84.3% (95% CI 81.4-87.3) and 86.1% (95% CI 83.4-89.0), respectively, with an adjusted HR 0.91 (95% CI 0.70-1.19, *P*= 0.51). Further, no significant overall or melanoma-specific survival differences were seen when comparing the pre- and the post-cohort in different subgroups depending on the age, sex or tumor characteristics. **Conclusions:** To our knowledge, this study is the first to assess the impact on overall survival from a national introduction of adjuvant treatment in stage III melanoma. In this nationwide, population and registry-based study, no survival benefit was detected in the cohort receiving adjuvant therapy. Considering also the significant side effects and costs, these findings encourage a careful assessment of the current recommendations on adjuvant treatment. To offer close follow-up, and only treat if relapse occurs, should be an option discussed with patients with fully resected stage III melanoma. Research Sponsor: Swedish Cancer Society, Region Stockholm, Radiumhemmets Forskningsfonder.

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9571 **Poster Session**

Population-based validation of the melanoma institute australia (MIA) and the memorial sloan-kettering cancer center (MSKCC) predictive tool for sentinel node status in patients with melanoma.

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Background: Patients with primary cutaneous melanoma are selected for sentinel lymph node biopsy (SLNB) based upon their risk of a positive SLN being identified. To improve upon stage-based categorization, the Memorial Sloan Kettering Cancer Center (MSKCC) and Melanoma Institute Australia (MIA) developed predictive models. Which model is more clinically useful is currently unclear. **Methods:** Consecutive patients undergoing SLNB from 2007-2021 were identified from the Swedish Melanoma Registry (SweMR), which covers 99% of patients with invasive cutaneous melanoma in Sweden. The predicted probability of SLN positivity was calculated using the MSKCC and limited MIA models (using mitotic rate as absent/present instead of count and excluding the optional variable lymphovascular invasion) for each patient. The operating characteristics of the models were assessed and compared. The "clinical utility" of each model was assessed using decision curve analysis (DCA) and compared with a strategy of performing SLNB on all patients. **Results:** In total 10,089 patients were included; the median Breslow thickness was 1.8 mm, 33.7% were ulcerated, and 1,802 patients had a positive SLN (17.9%). Both the MSKCC and limited MIA models were well calibrated across the full range of predicted probabilities, and had similar external area under curve (AUC), MSKCC 70.8% (95% CI 69.5-72.1%) and MIA 70.3% (95% CI 68.9-71.7%). When new models were constructed to compare the incremental value of the additional parameters of either nomogram over Breslow thickness alone, the AUCs were 70.1%, 71.6% and 72.0% for Breslow alone, MIA parameters and MSKCC parameters, respectively. At a risk threshold of 5%, DCA indicated no added net benefit for either model compared to performing SLNB for all patients. At risk thresholds of 10% or higher, both models added net benefit compared to SLNB for all. The greatest benefit was observed from use of the models in patients with T2 melanomas when a threshold of 10% was used to select patients for SLNB. In that setting, use of the nomograms led to a net reduction in seven avoidable SLNBs per 100 patients for the limited MIA nomogram and eight for the MSKCC nomogram, when compared to a strategy of SLNB for all. **Conclusions:** This study confirms the statistical performance of both the MSKCC and limited MIA models in a large, nationally-representative dataset. However, clinical utility as assessed by DCA demonstrated that using the models only improved selection for SLNB when a risk threshold of at least 10% was employed, and then mainly for T2 melanomas. Either further development of the nomograms, or other strategies, are needed to improve selection at lower risk thresholds. Research Sponsor: Knut and Alice Wallenberg Foundation, Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden.

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9572 **Poster Session**

Tumor-informed circulating tumor DNA (TI-ctDNA) based molecular residual disease (MRD) detection and relapse risk for patients with stage II-IV melanoma in surgical remission: A single center experience.

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Background: Melanoma is associated with significant risk of relapse after surgery. While the odds of relapse increase with advancing stage, long term relapse free survival (RFS) is possible without adjuvant therapy in a significant subset of patients as shown by AJCC v8 staging long term survival data. TI-ctDNA (Signatera™) is a non-invasive biomarker for MRD detection and functions by sequencing the patient's own tumor for the creation of a customized panel of PCR probes based upon a tumor's unique mutational profile. Positive TI-ctDNA testing is significantly associated with relapse after surgical resection in colorectal cancer and may help inform treatment decision-making, allowing for intensification or de-intensification of patient management. This study describes the operating characteristics of TI-ctDNA in monitoring for relapse in patients with resected melanoma. **Methods:** This is a single center retrospective analysis of patients with stage IIb-IV melanoma in surgical remission. Between January 2021 and January 2023, male and female patients presenting in surgical remission were monitored with TI-ctDNA at 6- or 12-week intervals. Surveillance imaging for relapse was performed according to standard of care guidelines appropriate for tumor stage. Patients were treated with immunotherapy, targeted therapy, or melanoma specific anti-tumor vaccine. Duration of RFS from surgery to detectable TI-ctDNA was recorded, along with duration of RFS from surgery to confirmed melanoma relapse. **Results:** 45 eligible patients were included in the analysis. 10 patients had detectable TI-ctDNA during the study period. 7 patients had confirmed relapse, 6 of whom were TI-ctDNA positive and 1 who was TI-ctDNA negative. The total relapse rate in TI-ctDNA positive patients (6/10) was significantly higher than the relapse rate in TI-ctDNA negative patients (1/35) [$p = 0.0002$]. Time to detection of positive TI-ctDNA was variable and ranged from 0 to 664 days (median 73 days). **Conclusions:** TI-ctDNA testing demonstrated preliminary ability to differentiate melanoma patients at the highest risk of relapse. Prospective evaluation of TI-ctDNA monitoring for determination of patients at high versus low risk of relapse is warranted and may help to inform future clinical trial designs by allowing for patient stratification to low risk (undetectable TI-ctDNA) and high risk (detectable TI-ctDNA) disease states. Research Sponsor: None.

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9573 **Poster Session**

Discovery and validation of AMBLor as a prognostic biomarker for non-ulcerated cutaneous AJCC stage I/II melanoma.

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Background: Cutaneous melanoma incidence continue to increase, with a particular increase in the number of patients diagnosed with thin, $<$ 1mm tumours with reduced probability of recurrence-free survival. The inability of current AJCC staging criteria to identify genuinely low risk subsets of patients with AJCC stage I/II tumours thus emphasises the acute need for credible prognostic biomarkers to stratify patient follow-up based on personalised risk. The combined immunohistochemical (IHC) expression of AMBRA1 and Loricrin (AMBLor) in the epidermis overlying non-ulcerated AJCC stage I melanomas has recently been identified as a prognostic biomarker and valuable pre SLNB test. The aim of the present study was to evaluate the potential for AMBLor as a prognostic biomarker for both AJCC stage I and II non-ulcerated melanoma. **Methods:** Prospective analysis of AMBLor was performed in two independent retrospective cohorts of non-ulcerated AJCC (8^{th} edition) stage I and II cutaneous melanomas derived from the USA and Australia (discovery cohort) and Spain and the UK (Validation cohort) following validated automated immune-histological staining and binary scoring analysis to define at risk vs low risk subgroups. Each cohort was powered to represent rates of 10% or up to 20% metastasis for stage I or stage II disease respectively. **Results:** Data revealed retention of AMBLor in the discovery cohort of 541 melanomas correlated with significantly increased recurrence-free survival (RFS) of 96% compared to 87% for patients with stage I/II melanomas in which AMBLor was lost (P = 0.06; HR 3.6, 95% CI 1.99-6.84, NPV 96%). Subsequent AMBLor analysis in the validation cohort of 303 tumours, further confirmed retention of AMBLor was associated with increased RFS of 98% compared to 81% for patients with stage I/II tumours in which AMBLor was lost (P = 0.01; HR 8.16, 95% CI 3.68-18.07). **Conclusions:** Collectively data from this multi-international study confirm AMBLor as a prognostic biomarker marker able to identify genuinely low risk subsets of AJCC stage I/II melanomas. Inclusion of AMBLor into clinical melanoma management may therefore aid stratification of patient follow up, enable significant savings on healthcare resources and improve patient anxiety. Research Sponsor: NIHR i4i funding, UK; AMLo Biosciences, A Newcastle University Spin out company.

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Intralesional therapy, limb infusion/perfusion, and immune checkpoint inhibitors as first-line therapy in surgically unresectable melanoma in-transit metastases.

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Background: Surgery remains the gold standard for resectable melanoma in-transit metastases (ITM). Unresectable ITM is a heterogenous disease with multiple treatment (tx) options including systemic therapies such as immune checkpoint inhibitors (ICI), regional therapies such as isolated limb infusion or perfusion (ILI/P), and intratumoral therapies such as talimogene laherparepvec (IT). Until now, there has been no direct comparison of these first-line tx for unresectable ITM. **Methods:** A retrospective chart review of patients (pts) with ITM treated first-line with IT, ILI/P, or ICI was performed at 11 institutions. Pts with unresectable ITM, synchronous nodal or distant metastatic disease were excluded. **Results:** 560 pts (54% women) were identified, 86 received IT, 353 received ILI/P, and 121 received ICI from 1990-2022. ICI pts were youngest, IT pts were oldest ($p<0.001$). Limb was the most common site of ITM. There was no difference in largest ITM size, but number of lesions (burden of disease (BOD)) was highest in ILI/P pts and lowest in IT pts (p=0.003). Toxicity (tox) requiring <90 days ($p<0.001$) or > 90 days (p=0.034) of pharmacologic tx as well as tox requiring hospitalization ($p<0.001$) was greatest in ICI pts. Lymphedema was more likely in ILI/P pts (p=0.016). Median follow-up was much longer for ILI/P pts at 8.0 yrs compared to 2.5 yrs for IT pts and 3.1 yrs for ICI pts. Overall response rate (ORR) was 82.2% in ILI/P pts, significantly higher than IT (72.1%, p=0.047) or ICI pts (63.6%, $p<0.001$). Overall survival was similar between modalities (p=0.167); however, ILI/P pts had worse progression-free survival (PFS) ($p<0.0001$) and melanoma-specific survival (MSS) (p=0.003). On multivariable analysis of MSS by number of ITM present, MSS remained worst if ILI/P was used for low BOD, ≤3 ITM (p=0.005), but no difference was seen between tx modalities for higher BOD, >3 ITM (p=0.211). **Conclusions:** ICI was used more often in younger pts with less BOD, IT in older pts with less BOD, and ILI/P in older pts with high BOD. Short and long-term tox was greater in ICI. ILI/P had the best ORR, but ICI and IT resulted in greater overall MSS. Multidisciplinary consideration of risks and benefits of each modality should guide ITM tx selection. Research Sponsor: None.

Patient and tumor characteristics, toxicity, and outcomes by treatment modality.

	IT n= 86	ILI/P n=353	ICI n=121	p-value
Age (yrs, median)	74	67	64	p<0.001
Number of ITM (mean)	4.2	12.6	7.1	p=0.003
Tox Requiring <90 Days Pharmacologic Tx (%)	18.0	20.4	44.1	p<0.001
Tox Requiring >90 Days Pharmacologic Tx (%)	0.0	12.7	16.9	p=0.034
Tox Requiring Hospitalization (%)	1.4	9.2	22.1	p<0.001
ORR (%)	72.1	82.2	63.6	IT vs. ILI/P p=0.047 ILI/P vs. ICI p<0.001 ICI vs. IT p=0.231
Median Follow-Up (yrs)	2.5	8.0	3.1	-
Median PFS (yrs)	2.1	0.7	1.2	p<0.0001
MSS (cumulative incidence, events/total)	13/ 85	148/ 347	15/ 106	p=0.003

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9575 **Poster Session**

Nature and management of melanoma recurrences following adjuvant anti-PD-1 (PD1) therapy.

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Background: Despite improved outcomes with the use of adjuvant PD1 therapy, approximately 50% of patients (pts) develop recurrent disease by 5 years. Data to define best management of recurrences is lacking, including whether retreatment with PD1 has benefit. **Methods:** This was a multicentre, international retrospective study of pts with resected stage II-IV melanoma who commenced adjuvant PD1 therapy before January 2022 and then recurred. Demographics, disease characteristics, treatment, toxicity, recurrence patterns, management and outcomes were collected. **Results:** 711 pts from 17 sites were included. Med age was 60 [range 16-92], 64% (N=451) were male. 641 (91%) pts were stage III (A 7%, B 24%, C 54%, D 3%), 18 (2%) stage II, 51 (7%) stage IV. 80% (N=536) underwent SLNB prior to PD1, of which 44% (N=236) went onto CLND. 635 pts (90%) received PD1, 74 (10%) PD1 + other. Med time to recurrence was 6.2 months (m) (0-68.5); 63% (N=444) recurred ON PD1, while 36% (N=257) recurred OFF. 338 pts (48%) recurred within 6m of starting adjuvant, 166 (23%) between 6-12m, 140 (20%) 12-24m and 59 (8%) after 24m. Initial recurrences were locoregional (LR) alone in 315 (44%), 307 (43%) distant alone, and 78 (11%) both. Patients with LR recurrences alone underwent definitive surgery, or surgery + radiation in 98 (31%) and 42 (13%) respectively. After initial LR management, 164 (52%) had a further local and 129 (41%) distant recurrence. Those with initial distant recurrences were managed with definitive surgery (21, 7%), surgery + radiation (8, 3%) and radiation alone (14, 5%). Further 'second' adjuvant therapy was given in 27% (N=86) of LR and 6% (N=25) of distant recurrences. Definitive systemic therapy at first recurrence was given in 77% (N=296) distant and 23% (N=73) LR recurrences (Table). **Conclusions:** Patients recurring after adjuvant PD1 therapy do so early, and often while on drug. Patients with resected recurrences often receive "second adjuvant" therapy, although whether adjuvant or definitive, outcomes are poor. Novel drug therapies and clinical trials are required for those who recur despite PD1 therapy. Research Sponsor: None.

Second adjuvant (N=119)	RFS2*†	DMFS2*†	PFS2*†	OS*
BRAF/MEKi (N=62)	24.9 (7.8-66.0)	16.2 (5.0-42.3)	15.3 (0.5-42.3)	23.4 (1.3-56.8)
PD1 (N=42)	11.7 (2.9-58.1)	3.7 (1.3-24.3)	9.0 (1.2-44.0)	19.9 (0.7-76.1)
(ON PD1; N=23)	3.2 (0.5-22.8)	18.1 (0.7-76.1)	6.8 (0.7-47.5)	27.0 (0.7-76.1)
(OFF PD1; N=19)	17.5 (2.6-52.5)	17.5 (2.6-72.7)	13.3 (2.9-61.2)	16.6 (5.5-72.7)
Definitive systemic therapy (N=378)	**ORR (%)**	**DOR***	**PFS***	**OS***
PD1 alone (N=46)	24	6.3 (2.7-14.4)	17.4 (2.3-44.3)	15.2 (1.0-69.7)
(ON PD1, N=18)	17	11.9 (9.8-14.0)	9.4 (1.4-54.8)	21.3 (3.0-54.8)
(OFF PD1, N=28)	32	-	7.9 (2.7-34.0)	11.5 (3.3-51.1)
CTLA4 alone (N=19)	11	-	9.8 (4.9-50.5)	12.7 (2.0-35.7)
CTLA4 + PD1 (N=157)	34	5.6 (0-21.7)	13.5 (1.9-55.3)	14.4 (1.0-69.7)
BRAF/MEKi (N=105)	65	3.4 (0-29.3)	14.8 (0.6-73.5)	15.6 (1.3-67.4)

*Med (range), m. †From start of second adjuvant, m.

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9576 **Poster Session**

NEO-CESQ study: Neoadjuvant plus adjuvant treatment with cemiplimab in surgically resectable, high risk stage III/IV (M0) cutaneous squamous cell carcinoma.

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Background: In the last years, the treatment of locally advanced and/or metastatic cutaneous squamous cell carcinoma (CSCC) has been revolutionized by the introduction of cemiplimab, an anti-PD-1 antibody, which showed a 50% overall response rate and long term benefit (1). Recently, a phase II trial of neoadjuvant cemiplimab in resectable CSCC patients (2), showed a major pathological response (MPR) rate of 63.3%. In the current multicenter, phase II trial we evaluated the efficacy of neoadjuvant plus adjuvant immune checkpoint inhibitor in patients with surgically resectable, high-risk stage III/IV (M0) CSCC. **Methods:** Patients with surgically resectable high-risk stage III/IV (M0) CSCC received cemiplimab at a dosage of 350 mg every 3 weeks for two cycles prior surgery and for one year after surgery. The study primary endpoint was MPR [pathological complete response (pCR) or near pCR ($<$ 10% remaining viable tumour cells in the surgical pathology sample)] per independent central pathology review. Key secondary endpoints included recurrence-free survival (RFS), overall survival (OS), safety and the analysis of predictive biomarkers. **Results:** From May 2021 to October 2022 twenty-three patients were enrolled in 6 centers. pCR was observed in 9 (39%) patients and near pCR in 2 (8%) patients, while pathological partial response (10-50% remaining viable tumour cells) and no pathologic response was observed in 1 patient and 11 patients, respectively. At data lock of 31st January 2023, only one patient was discontinued due to clinical progression. Furthermore, it was observed n = 60 (57%) any adverse events (AE) and n = 29 (30%) treatment-related AE. No any G3/G4 AE were observed. **Conclusions:** Neoadjuvant cemiplimab induced a pathological response in 52% of stage III/IV (M0) CSCC patients with a MPR in 48%. The study is still ongoing to evaluate the impact of combined neoadjvuant and adjuvant immunotherapy on RFS and biomarkers analysis. Clinical trial information: NCT04632433. Research Sponsor: SANOFI.

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9577 **Poster Session**

Association of circulating tumor DNA kinetics with disease recurrence in patients with stage IIIB/C/IV melanoma treated with adjuvant immunotherapy in Checkmate 238.

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Background: In patients (pts) with resected, stage III/IV melanoma receiving adjuvant immunotherapy, pre-treatment (pre-Tx) and on-treatment (on-Tx) circulating tumor DNA (ctDNA) combined with tumor features were evaluated to predict recurrence risk. **Methods:** We used analytically validated, mutation-specific droplet digital PCR (ddPCR) assays to measure ctDNA in pre- and on-Tx plasma samples from pts with resected stage IIIB/C/IV melanoma enrolled in CheckMate 238 (NCT02388906) receiving either adjuvant Nivolumab (NIVO) or Ipilimumab (IPI). Assay choice was based on detection of one of the 7 melanoma hot-spot mutations in pt tumors: BRAF V600E/K, NRAS Q61R/L/K, or TERT C228T/C250T. We evaluated associations between ctDNA detection, recurrence free survival (RFS), distant metastasis free survival (DMFS), and known immunotherapy tumor biomarkers including PD-L1, IFNg gene signature, CD8, and tumor mutational burden. Associations between ctDNA kinetics and RFS/DMFS were analyzed using Kaplan-Meier and Cox regression models. **Results:** Mutations were identified in 87% of tumors. ctDNA was detected in pre-Tx samples from 94/753 (12.5%) pts. Pre-Tx ctDNA was significantly associated with higher stage of disease, LDH $\geq$ ULN, PD-L1 $<$ 5%, and tumor IFNg-RNA signature expression below the median. Detection of pre-Tx ctDNA was associated with shorter RFS and DMFS in both NIVO and IPI arms compared to undetectable ctDNA (Table). ctDNA detection on-Tx (week (w) 3, 7, 13, 25, 37, 49) was also associated with shorter RFS. Refined subgroup predictions that potentially impact therapy were achieved by incorporating pre- and on-Tx time points. Of those with baseline and w7 ctDNA results, pts in the NIVO arm with undetectable pre-Tx ctDNA (n=308) that became positive at w7 (n=22) had shorter RFS (median RFS 20.68 mos [95% CI, 2.79, NR]) than pts in whom on-Tx ctDNA remained undetectable (n=286) (median RFS, NR [95% CI, 61.1, NR]). Pts with positive pre-Tx ctDNA (n=42) that remained positive at w7 (n=23) had markedly shorter RFS (median RFS, 3.35 mos [95% CI, 2.73, 20.44]) vs pts in whom on-Tx ctDNA became undetectable (n=19) (median RFS, NR [95% CI, 14, NR]). Similar results were observed in the IPI arm. **Conclusions:** Pre- and on-Tx ctDNA measurements are associated with melanoma recurrence risk during adjuvant checkpoint inhibitor therapy. Incorporation of ctDNA with other tumor molecular features may improve prediction of RFS and DMFS in this setting. Clinical trial information: NCT02388906. Research Sponsor: U.S. National Institutes of Health; Bio-Rad; Bristol Myers Squibb.

	Patients, n	Pre-treatment ctDNA status	Median RFS, mos (95% CI)	RFS HR (95% CI)	Median DMFS, mos (95% CI)	DMFS HR (95% CI)
NIVO	49	+	16.7 (4.7, 41.6)	2.09 (1.43, 3.06)	24.48 (8.54, NR)	2.27 (1.51, 3.42)
	327	-	NR (61, NR)		NR (NR, NR)	
IPI	45	+	5.91 (2.86, 15.90)	2.17 (1.49, 3.18)	6.70 (2.92, 22.08)	2.59 (1.75, 3.84)
	332	-	30.9 (19.8, 54.5)		NR (52, NR)	

CI, confidence interval; HR, hazard ratio; NR, not reached.

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9578 **Poster Session**

Melanoma disparities in urban vs rural communities in the era of immunotherapy: An NCDB analysis.

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Background: Several barriers to care exist for melanoma patients including distance to specialty care, transportation, and cost. Additionally, differences in rural and urban melanoma incidence have not been fully investigated. Using a large nationwide database, we aim to investigate the relationship between urban and rural locations in stage of melanoma presentation and access to adjuvant systemic treatment. **Methods:** The National Cancer Database (NCDB) was queried for all adult patients ($\geq$ 18 years old) with diagnosis of cutaneous melanoma from 1/1/2011 – 12/31/2020. For receipt of adjuvant immunotherapy, diagnosis from only 1/1/2017 - 12/31/2020 was analyzed. Demographic, socioeconomic, tumor-related, and treatment-related factors were analyzed using SPSS Statistics, with Chi-square analysis performed for categorical variables and ANOVA performed for continuous. **Results:** Between 2011 and 2020, 558,445 patient cases were identified and included in the analyses. The average age was 63.7 years, and patients predominantly identified as White (97.6%) and non-Hispanic (96.2%). Patients in urban areas were more likely to present with melanoma of the extremities (40.8% vs 36.2%, $p < 0.001$), while patients in rural areas presented with head and neck melanoma (26.2% vs 31.0%, $p < 0.001$). Additionally, patients in urban areas were more likely to have an early-stage melanoma (0, 1, or 2) melanoma (51.4% vs 48.5%, $p < 0.001$). Patients in rural areas traveled an average of 68 miles for care, in contrast to urban patients who traveled an average of 20 miles ($p < 0.001$). There was no significant difference when comparing receipt of immunotherapy for stage 3 or stage 4 patients. **Conclusions:** In rural areas, patients with melanoma tended to present with a higher portion of head and neck melanoma and of later stage. Rural patients also had to travel farther for care. However, these differences did not result in fewer patients in rural areas receiving immunotherapy for appropriate treatment. Further studies are needed to evaluate how these presentation differences influence care outcomes. Research Sponsor: None.

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9579 **Poster Session**

A pilot study of the neoadjuvant use of vemurafenib plus cobimetinib in patients with BRAF-mutant melanoma with palpable lymph node metastases: Survival results.

Teresa M. Petrella, Catalin Liviu Dragos Mihalcioiu, Carolyn Nessim, Alan Spatz, Ian Watson, Frances Catriona Wright; Sunnybrook Hospital, Toronto, ON, Canada; Royal Victoria Hospital/Glen Site/Cedar Cancer Centre, Montreal, QC, Canada; Department of Surgery, University of Ottawa-Ottawa General Hospital, Ottawa, ON, Canada; Jewish General Hospital, Lady Davis Institute, McGill University, Canada, Montréal, QC, Canada; McGill University, Montreal, QC, Canada; Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: Melanoma patients with palpable nodal metastases have a very poor prognosis with the majority recurring within the first 2-3 years post-resection with survival ranging from 20-50% at 5 years. We aimed to ascertain if patients with a BRAF V600 mutation that receive vemurafenib and cobimetinib before surgery (neoadjuvantly) have a higher probability of resectability, pathologic complete response (pCR), and a lower risk of local recurrence and a longer disease free survival (DFS), distant metastatic free survival (DMFS) and overall survival (OS). **Methods:** This was a single arm, prospective, multi centre phase II study in patients with histologically confirmed, BRAF V600 mutated Stage IIIB and IIIC melanoma (AJCC 7th Edition) with palpable nodal disease. Patients received vemurafenib 960mg PO BID and cobimetinib 60mg PO OD for 4 months prior to resection followed by 8 months of adjuvant therapy post-surgery. CTscans were performed at baseline and before resection and every 6 months for the first 3 years and yearly in year 4 and 5. Biopsies for correlative studies and diagnosis were performed at baseline prior to starting therapy. The primary outcomes were the proportion of patients achieving resectability, radiologic response as per RECIST and the proportion of patients achieving a pCR. Presented here are the LRFS, DMFS, DFS and OS. **Results:** Twenty-four patients were enrolled and received neoadjuvant vemurafenib and cobimetinib and 21 underwent resection. Following resection and pathological evaluation 12 (57%; 95% CI 34.02-78.18)) patients achieved a pCR, 8 (38%; 95% CI 18.11-61.56) had a partial pathologic response and 1 had no pathologic response. Of the 24 patients, 2 patients (8%) developed local recurrence, 6 patients (25%) developed distant metastasis, and 8 patients (33%) had either local or distant recurrences. 7 patients (29%) died due to metastatic disease. At 60 months, LRFS was 89.5% (76.7-100%), DMFS was 75.0% (59.5-94.5%), DFS was 85.7% (72.0-100%), and OS was 63.9% (95% CI 43.5-93.8). Among total 20 evaluable patients, 17 patients had CR/PR and 3 had PD/SD as best response. There was no significant difference between patients with CR/PR or SD/PD (log-rank p-value = 0.0548) with 48 month survival of 82.4% for CR/PR population compared to 33.3% with SD or PD. **Conclusions:** In this small phase II study, neoadjuvant vemurafenib and cobimetinib led to a higher LRFS, DMFS, DFS and OS of all resected patients with bulky nodal disease compared to historical survival rates. Clinical trial information: NCT02036086. Research Sponsor: Roche; institutional funding.

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9580 **Poster Session**

Prognostic significance of immune-related adverse events and immunosuppression in patients with melanoma receiving adjuvant anti-PD-1 therapy.

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Background: Treatment with anti-Programmed Death-1 (PD-1) therapy reduces the risk of recurrence for patients (PT) with resectable Stage IIB-IV melanoma (MEL). This treatment is associated with the development of immune-related adverse events (irAEs), which may necessitate use of immunosuppressive therapy and treatment discontinuation. This project investigates the impact of irAE and immunosuppressive therapy in survival outcomes of PTs with MEL. **Methods:** PTs with stage IIB-IV resectable MEL who received adjuvant or neoadjuvant treatment with anti-PD-1 therapy were enrolled from the University of Pittsburgh Melanoma Center biospecimen repository. The association between irAEs/immunosuppressive therapy and recurrence-free survival (RFS) and overall survival (OS) were evaluated by univariate and multivariate Cox proportional hazards regression models. **Results:** A total of 6059 PT were consented to the repository: stage III = 1,328, stage IIB = 403, and stage IIC = 269 PT. Of these PT, 180 men and 93 women received adjuvant anti-PD-1 therapy. Average age at diagnosis was 61. BRAF mutation present in 94 PTs: V600E = 71 PT, V600K = 11 PT. Documented irAEs occurred in 50.9% of PTs. Cutaneous irAEs were most common (65/139, 46.8%), followed by endocrine (45/139 32.4%), and visceral organ (37/139, 26.6%). Of the 32 visceral organ irAEs, 15 were gastrointestinal, 10 pulmonary, 5 hepatic, and 1 renal. Systemic corticosteroids $>$ 10mg of prednisone equivalent were administered during adjuvant therapy for 24.9% of PT. In the univariate model, development of irAEs was associated with improved OS (HR = 0.38; CI 0.18-0.83, p = 0.015). In a multivariate analysis after adjusting for age and sex, irAE development continued to be associated with improved OS (HR = 0.38; CI 0.17-0.82, p = 0.014). RFS did not differ for patients that developed irAEs (HR = 0.9; CI 0.59-1.4, p = 0.67). Steroid treatment was not associated with a change in OS (HR = 1.04; CI 0.46-2.4, p = 0.93) or RFS (HR = 0.96; CI 0.59-1.56, p = 0.87). **Conclusions:** Half of stage IIB-IV resectable MEL PT receiving adjuvant anti-PD1 therapy developed irAEs, of which 24% required steroid therapy. Development of irAE was associated with improved OS and corticosteroid use for irAE did not mitigate adjuvant therapy outcome benefits. Research Sponsor: None.

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9581 **Poster Session**

Intralesional oncolytic virotherapy with talimogene laherparepvec in patients with cutaneous lymphomas and non-melanoma skin cancers.

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Background: Cutaneous lymphomas (CL) and non-melanoma skin cancers (NMSC) present with skin lesions and can often be treated with local therapies. However, some do not respond or relapse, underlining the need for new treatment options. Intralesional oncolytic virotherapy with genetically modified Herpes simplex 1 virus called Talimogene laherparepvec (T-VEC) was approved for cutaneous melanoma. Given previous reports on oncolytic virotherapy in non-melanoma tumors, we investigated the effect of intralesional T-VEC in patients with CL and NMSC. **Methods:** Patients with CL and NMSC without extracutaneous spread were eligible (NCT03458117). They were treated according to the standard for up to 8 injections. We assessed clinical response of injected and, whenever possible, non-injected lesions using response criteria for intratumoral therapies (itRECIST). Safety was assessed using CTCAE v5 criteria. To evaluate T-VEC induced changes, we collected tumor biopsies at baseline, after 2 and 5 injections. We performed multiplex immunohistochemistry for CD3, CD8, CD79a, CD56, CD11c and FoxP3 and evaluated the changes using Akoya Bioscience technology. **Results:** Twenty-seven patients were enrolled into the study: 19pts with cutaneous B-cell lymphoma (CBCL), 5pts with cutaneous T-cell lymphoma, 1pt with cutaneous squamous cell carcinoma and 1pt with Merkel cell carcinoma. The mean age was 61.9yrs. In total, 26pts have received at least one intralesional T-VEC, one patient has withdrawn consent before the first infusion. Patients received median of 7 injections, 11pts (44%) have received 8 planned injections. Therapy was well tolerated with treatment related fever, flu-like symptoms and ulceration of the injected tumor being the most common treatment related adverse events (AE) (34% each). Three patients (12%) had grade 3 AE. Of the injected lesions, 84% demonstrated response, with reduction of the elevation in 84% and reduction of redness of the tumor in 68%. Non-injected response was 40% and overall response was 32%. Tissue samples of 18pts were available for analysis. Following T-VEC injections, responding lesions had an increase of CD8+ and decrease of FoxP3+ cells, while all lesions had an increase of CD56+ cells and slight reduction of CD79a+ cells. Responding CBCL samples had increased CD3+ cells, whereas all samples had an initial reduction of CD79a+ and CD11c+ cells, independent of response. **Conclusions:** Oncolytic virotherapy with intralesional T-VEC induces clinical responses and is tolerated without any unexpected toxicities in patients with locally advanced cutaneous lymphomas and NMSC. T-VEC induces activation of immune response, with differences in responding and non-responding lesions. T-VEC represents a viable treatment option for patients with CL and NMSC, and should be investigated in larger controlled clinical trials. Clinical trial information: NCT03458117. Research Sponsor: Amgen.

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9582 **Poster Session**

Longitudinal circulating tumor DNA monitoring for detection of molecular residual disease in patients with surgically resected stage II/III melanoma.

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Background: Over the past decade, advances in immunotherapy (IO) have dramatically improved overall survival (OS) for patients with metastatic melanoma. Immune checkpoint inhibitors and BRAF/MEK inhibitors also became standard of care for surgically resected stage III melanoma, and most recently pembrolizumab was approved for stage IIB/C patients. Although the phase III trials that led to their respective approvals met their primary endpoints for relapse-free survival, no benefit in OS has been observed. Given that a large proportion of early-stage melanoma patients are cured with surgery alone, the decision to proceed with adjuvant therapy should be weighed against the risk of potential life-altering toxicity. There is a high unmet need to develop biomarkers to accurately select patients who are most likely to benefit from adjuvant IO while sparing a group of low risk patients from unnecessary treatment. In this study, we evaluated the prognostic value of personalized, tumor-informed circulating tumor DNA (ctDNA) testing in patients with resectable stage II/III melanoma. **Methods:** In this real-world study, longitudinal plasma samples (n = 159) were analyzed in real-time from 45 stage IIA-IIID cutaneous melanoma patients treated at Rush University between 03/30/2021 and 01/12/2023. A personalized, tumor-informed ctDNA assay (Signatera bespoke, mPCR-NGS assay) was used for detection and quantification of ctDNA in plasma samples. **Results:** Personalized, tumor-informed ctDNA assays were successfully designed for 93% (42/45) of patients using tissue samples from either surgical resection (14/42, 33%) or biopsy (26/42, 67%; 16 shave, 10 excisional, 1 punch, 1 core). ctDNA was detectable at one or more time points in 36% (15/42) of patients. We observed a higher ctDNA-positivity rate in stage III patients (11/20, 55%) compared to stage II patients (4/22, 18%). Twelve of the 15 ctDNA-positive patients received adjuvant IO/treatment escalation after a positive ctDNA result; 6 patients had sustained ctDNA clearance, 2 had transient clearance, and 4 continue to receive adjuvant IO and follow-up ctDNA testing. Radiographic recurrence was observed in 7/42 patients, 6 of whom were ctDNA-positive. Ninety-six percent (26/27) of patients with persistent ctDNA-negativity remain clinically and radiographically progression-free. **Conclusions:** Our data suggest that molecular residual disease detection using a personalized, tumor-informed ctDNA assay is highly prognostic in melanoma patients undergoing curative resection. Sustained clearance of ctDNA was achieved with adjuvant therapy in a subset of this cohort. Prospective studies evaluating the utility of ctDNA to aid clinical decision-making regarding adjuvant treatment intensification or de-escalation are warranted. Research Sponsor: None.

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9583 **Poster Session**

Expanded cohort and extended follow-up of neoadjuvant plus adjuvant (neo + adj) dabrafenib (D) and trametinib (T) in patients (pts) with surgically resectable stage (stg) III/IV melanoma.

Tarin Hennegan, Elizabeth M. Burton, Lauren Simpson, Victor Gerardo Prieto, Merrick I. Ross, Isabella Claudia Glitza, Lisa G Beal, Jeffrey E. Gershenwald, Hussein A. Tawbi, Michael K.K. Wong, Zhongya Wang, Roland L. Bassett, Anthony Lucci, Jeffrey Edwin Lee, Sarah B. Fisher, Sapna Pradyuman Patel, Jennifer Leigh McQuade, Michael A. Davies, Jennifer Ann Wargo, Rodabe Navroze Amaria; MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Most melanoma pts are diagnosed with earlier-stage, surgically resectable disease. Although there are approved adjuvant immunotherapy (IT) and targeted therapy (TT) options available, neoadjuvant systemic treatment (NST) has demonstrated improved outcomes based on pathologic complete response (pCR). We previously reported outcomes from a randomized trial comparing neo +adj DT vs upfront surgery followed by adj DT in pts with surgically resectable stage III/IV BRAF mutated melanoma. After enrolling 21 pts, the randomized study was closed by the Data Safety Monitoring Board due to rapid disease progression in pts randomized to upfront surgery. The trial continued as a single-arm study to evaluate neo + adj DT. With a median follow up of 35 mos (range 6-97 mos), we report the updated outcomes for the pts evaluable for the primary endpoint. **Methods:** We conducted a single-center, phase II clinical trial (NCT02231775) evaluating neo + adj DT in pts with surgically resectable, RECIST measurable clinical stg III or oligometastatic stg IV BRAF V600E/K mutated melanoma. Study objectives included determination of pCR and survival outcomes based on INMC path response. Pts received oral D 150mg BID and T 2mg daily for 8 wks prior to surgery and 44 wks of adjuvant DT starting 1wk post-surgery. Imaging was performed prior to surgery to determine the RECIST 1.1 objective response rate (ORR) and then every 12 wks to monitor for recurrence. **Results:** Of the 51 pts who received neo DT, 49 were considered evaluable for the primary endpoint unrelated to progression prior to surgery. Median age was 56 (IQR 45-66). 10 pts received prior adj IT. All but 1 pt underwent surgery on time with delay due to treatment related toxicity. The radiographic ORR was 78%, including 6 (12%) CR. 17 (35%) pts achieved a pCR, 7 (14%) near pCR, 12 (24%) partial path response, and 13 (27%) path non-response. 47 (96%) pts initiated adj treatment; 23 (47%) completed all planned adj treatment, 7 (14%) discontinued adj treatment due to recurrence and 12 (24%) due to toxicity. Median RFS for all pts was 17.6 mos (95% CI: 14,40.1) and was improved for pts with pCR versus non-pCR [median Not Reached (NR) vs 11.3 mos; p = 0.0002]. Median distant metastasis free survival (DMFS) for all pts was 48.9 mos (95% CI: 24.1, NA) and was also improved for pCR pts (median NR vs 17.5 mos; p = 0.0004). Median OS was not reached for all pts and was improved in pCR pts (p = 0.03). No new safety signals were seen. **Conclusions:** Neo + adj DT is feasible and safe in pts with surgically resectable BRAF mutated melanoma. With a median follow-up of 35 mos, median RFS, DMFS, and OS have not been reached for pts with a pCR after neo DT, and are all significantly prolonged compared to non-pCR pts. These results demonstrate durable benefit for neo + adj DT in this high-risk pt population that achieve a pCR. Clinical trial information: NCT02231775. Research Sponsor: Novartis; Melanoma Research Alliance and Rising Tide Foundation.

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[^{18}F]FDG-PET to identify pathological responses upon neoadjuvant immune checkpoint blockade in cutaneous squamous cell carcinoma.

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Background: To improve clinical prospects of patients with locally advanced cutaneous SCC (CSCC), we tested the efficacy of neoadjuvant nivolumab with or without ipilimumab prior to standard of care curative surgery ± radiotherapy; the MATISSE trial (NCT04620200). Neoadjuvant immunotherapy-response prediction via FDG-PET imaging was demonstrated feasible in the IMCISION trial (PMID 34937871), where a decrease of ≥12.5% in total-lesion glycolysis (TLG) upon immunotherapy identified deep pathological responders to immunotherapy in head and neck SCC prior to surgery with 95% accuracy. The current research investigates the predictive power of FDG-PET to identify deep pathological responses to neoadjuvant immunotherapy in MATISSE patients. **Methods:** 26 patients with primary CSCC (stage I–IVa) were treated with neoadjuvant nivolumab with (n = 14) or without (n = 12) ipilimumab (weeks 0 and 2). FDG-PET/CT scans were evaluable at baseline and shortly before surgery (week 4) in 20 patients. Images were analysed for SUV_{max}, metabolic tumor volume (MTV), and TLG. Responders to immunotherapy were defined as having a major or partial pathological response to immunotherapy (MPR and PPR, showing ≤ 10% and 11-50% remaining viable cancer cells at time of surgery, respectively). **Results:** Overall, median SUV_{max}, MTV, and TLG decreased upon immunotherapy at the primary tumor site in responders (n = 15),whereas median SUV_{max}, MTV and TLG increased in non-responders (Table). Three patients with stable or increased SUV_{max}, MTV and TLG, also showed a pathological response and were classified as pseudo-progressive. Another patient with a MPR had an increase in SUV_{max}, but a decrease in MTV and TLG. All patients with any decline in SUV_{max}, MTV or TLG at the primary tumor site showed a pathological response (PPV 100%) and none of them developed a relapse at median follow-up 9.0 months. **Conclusions:** Primary tumor response assessment using FDG-PET-based ΔSUVmax, ΔMTV and ΔTLG accurately identifies pathological responses early upon neoadjuvant immunotherapy in cutaneous SCC. FDG-PET could, upon validation, select CSCC patients for response-driven treatment adaptation in future trials. FDG-PET-CT upon neoadjuvant immunotherapy in CSCC, changes in PET-parameters and predictive values of any decline in SUV_{max}, MTV or TLG. Clinical trial information: NCT04620200. Research Sponsor: The MATISSE trial is an investigator-initiated phase-2 clinical trial, partly funded bij Brystol-Myer-Squibb (BMS) and KIKI-foundation (private).

	Responders n=15	Non-responders n=5	*p*-value	PPV (%)	NPV (%)	Sens (%)	Spec (%)
ΔSUV_{max} median (range)	-32.5 (-78.9 – +230.8)	+15.2 (+1.0 – +50.3)	0.02[a]	100	55	73	100
ΔMTV median (range)*	-95.4 (-100.0 – +90.0)	+187.0 (+14.1 – +272.0)	<0.002[a]	100	57	77	100
ΔTLG median (range)*	-95.8 (-100.0 – +69.6)	+215.7 (+19.9 – +312.8)	<0.002[a]	100	57	77	100

[a] = p-values calculated with Mann-Whitney U test. PPV = positive predictive value, NPV = negative predictive value, Sens = sensitivity, Spec = specificity. *based on 13 responders and 4 non-responders.

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9585 **Poster Session**

FDG-PET/CT response and prediction of pathological response to neoadjuvant nivolumab and ipilimumab for clinical stage III melanoma.

Milton Jose De Barros E Silva, Monique Celeste Tavares, Joao Paulo S. N. Lima, Antonio C. Buzaid, Daniel Garcia, Veridiana Pires De Camargo, Andre Molina, Eduardo Bertolli, Matheus Lobo, Alexander Christopher Jonathan Van Akkooi, Clovis Pinto, Rafaela Brito De Paula, Eduardo Lima, José Augusto Rinck, Joao Duprat; A.C. Camargo Cancer Center, São Paulo, Brazil; A.C. Camargo, São Paulo, Brazil; Hospital Beneficência Portuguesa de São Paulo, São Paulo, Brazil; Beneficencia Portuguesa, São Paulo, Brazil; AC Camargo Cancer Center, Sao Paulo, Brazil; Melanoma Institute Australia, Wollstonecraft, NSW, Australia

Background: Neoadjuvant immunotherapy with nivolumab 3mg/kg and ipilimumab 1 mg/kg (N3+I1) for two cycles for clinical stage III melanoma have shown rates of major pathological response (MPR) of approximately 60%.The prognosis of this group seems to be excellent so far. On the other hand, patients classified as pathological non-responders have a worse outcome and early identification of this group may allow us to tailor the treatment before surgery. **Methods:** We conducted a multicenter retrospective analysis of patients with clinical stage III melanoma treated with neoadjuvant N3+I1 for two cycles who did baseline and pre-operative 18F-FDG-PET/CT. The total number of FGD avid lesions and the percentual difference between the maximum SUV per lesion was calculated. The pathological results were correlated to FGD-PET/CT findings. **Results:** Between January 2019 and January 2023, 28 patients with clinical stage III melanoma treated with N3+I1 who had baseline and preoperative 18F-FDG PET were identified. Gender: 20 (71%) males, median age (range):55 (34-78), BRAFV600E/K mut: 15(53%), positive nodes on baseline PET/CT:1 = 26 (92%), 2 = 1(4%), and 3 = 1(4%). All known lesions identified by CT scan were also captured by FGD-PET/CT. Site of node(s): axilla = 12 (43%), cervical = 10 (36%), and inguinal = 6(21%). All but one patient received 2 cycles of N3+IP1(1 patient had grade 3 toxicity and received only one cycle). Pathological response: MPR = 19(68%), non-MPR: 8 (28%), and 1(4%) did not undergo surgery due to widespread progression. An increase in maximum SUV and/or appearance of new lesion(s), n = 8(28%), was correlated to non-MPR or metastatic disease in all cases, including a patient who developed sarcoidosis-like reaction with increase of SUV in the index lesion (+68%) and appearance of inflammatory mediastinal lymph-nodes. The median increase was (range): +73% (+11% to 483%). Reduction or stable maximum SUV with no appearance of new lesion, n = 20 (72%), was associated with MPR in 19 patients (95%). One patient,who had G3 colitis (with the need of infliximab), had 32% of reduction in maximum SUV but 100% of viable tumor cells on pathological report. The median decrease (range) was -76% (-1.2% to -100%). **Conclusions:** FGD-PET/CT may help to predict pathological response in patients with clinical stage III melanoma who undergo to neoadjuvant nivolumab and ipilimumab. Research Sponsor: None.

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9586 **Poster Session**

Successful management of Australian patients with locally advanced keratinocyte cancer (KC) and/or extensive skin field cancerization (ESFC), using widefield volumetric arc radiation therapy (VMAT): Report with 24-month follow-up.

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Background: Keratinocyte cancer (KC) diagnoses are associated with an elevated risk of developing new skin lesions. Patients with extensive skin field cancerization (ESFC) have large areas (generally $\geq$50cm^2) of actinic keratoses and often, frequent keratinocyte cancers, necessitating repeated interventions. Volumetric modulated arc radiation therapy (VMAT) can precisely target large, complex surfaces with modulated doses, as required, leading to its increasing application to ESFC +/- KC. This is a follow-up 24-month report on the efficacy, safety, cosmetic, and quality of life outcomes of VMAT in the management of patients with ESFC +/- KC at Australian facilities. **Methods:** Two hundred and twenty-four fields for 194 patients with ESFC +/- KC have been prescribed widefield VMAT and prospectively enrolled in the National (Australian) Dermatology Radiation Oncology Registry (NDROR). One hundred and six fields are now beyond 24-months post-treatment. Over 80% of patients had received up to 4 prior non-radiotherapy interventions. Fields included lower and upper limb, face, scalp, or trunk regions. 3-, 6-, 12-, 18-, and 24-month follow-up assessments rated the percentage of field clearance, lesion response, new lesion events, cosmesis using the Lovett's scale, toxicity based on CTCAE, and quality of life as assessed using a EQ-5D-5L visual analogue scale (VAS). **Results:** Median dose delivered to ESFC-only and ESFC + KC fields were 45 Gy (16.2-60 Gy) and 47 Gy (22-60 Gy), respectively, in 25 daily fractions (7-30) across 7 weeks (2-13). At 24-month follow-up of 106 fields, 96% and 94% of ESFC-only and ESFC + KC fields, respectively had clinical success, defined as $>$ 90% field clearance. Cosmesis was graded excellent or good in 98% of fields. The incidence of new KC within the field out to 24-months was 11%. Grade 1-2 radiation dermatitis was induced in all fields during treatment, but resolved by 3-month follow-up. Six percent of fields exhibited grade 3 dermatitis. Twelve percent of patients discontinued treatment due to acute toxicities (Median 88% dose delivered). The most common persistent toxicity at 24-month follow-up was localized grade 1-2 xerosis (51%), alopecia (43%), and/or pruritis (8%). Quality of life was sustainably improved in patients at 24-month follow-up (3.67; p= 0.026). **Conclusions:** Widefield VMAT has a promising profile of clinical efficacy, safety, and cosmesis in patients with ESFC +/- KC for whom other therapies had failed. Treatment was also associated with significant and durable improvements in quality of life. While long-term follow-up of patients continues, these results provide further support for widefield VMAT as a suitable option for patients with increasingly unmanageable presentations of ESFC and locally-advanced KC. Clinical trial information: ACTRN12618000627257. Research Sponsor: GenesisCare.

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9587 **Poster Session**

Comprehensive genomic profiling (CGP) of clinically advanced and metastatic cutaneous adnexal carcinomas (CAs; MCADCA): A genomic landscape study.

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Background: Cutaneous adnexal tumors are a large group of malignant neoplasms that exhibit morphologic differentiation towards one of the four primary adnexal structures present in normal skin: hair follicles, sebaceous glands, sweat-apocrine glands, and sweat-eccrine glands. **Methods:** 276 cases of MCADCA underwent hybrid capture-based CGP to evaluate all classes of genomic alterations (GA). Microsatellite instability (MSI) status, tumor mutational burden (TMB), genomic loss of heterozygosity (gLOH), genomic ancestry prediction and COSMIC genomic signature were determined from sequencing results. PD-L1 was measured by IHC (TPS; Dako 22C3). Fisher exact method was used for statistical analysis with the false discovery rate corrected using Benjamini-Hochberg adjustment. **Results:** Sequencing was performed on the primary cutaneous tumor in 131 (47.4%) and on a local recurrence or metastatic site biopsy in 145 (52.5%) MCADCA. Male preponderance (64-81%) and age distributions mean (59-63 yrs) were similar in all groups with apocrine (APO) older than eccrine (ECC) (72 vs 62 yrs; p = .001). There were 173 (62.7%) sweat gland (SWT) derived, 55 (19.9%) were sebaceous gland (SEB) derived, 14 (5.1%) were hair follicle (HRF) derived and 34 (12.3%) were unclassified (UNK). 150/173 (86.7%) of SWT were ECC and 23 (13.3%) were APO. The SWT cases included 12 (6.9%) digital papillary ca's (DPA), 11 (6.3%) mucinous ca's (MAC), 19 (11.0%) poroca's (POR), 14 (8.1%) spiradenoca's (SPR), 10 (5.8%) syringoadenoca's (SRNG) and 77 (44.5%) unclassified ca's (UNC). GA/tumor were highest in SEB vs SWT (7.9 vs 4.9; p = .004) and lowest in DPA (2.1 vs 5.0 non-DPA; p = .03). There we no ancestry distribution differences. When compared with the SWT group, the SEB group had higher frequencies of *RB1* GA (38.2% vs 8.1%; $p < .0001$) and *TP53* GA (76.4% vs 43.4%; p = .0002) indicating likely neuroendocrine differentiation. The MAC group had significantly higher *PTCH1* GA than the non-MAC group (36.4% vs 1.8%; p = .044). MSI-High status was highest in the SEB group vs all other groups (SEB 15.7% vs SWT 1.2%; p = .005). gLOH $>$ 16% was most frequent in SEB when compared with SWT (19.6% vs 7.2%; p = .081). The MMR signature was more frequent in SEB than SWT (32.0% vs 2.1%; p = .005). The mean TMB was high in all MCADCA ranging from 10.4 mut/Mb in HRF to 38.8 mut/Mb in MAC with the exceptions of APO (2.7 mut/Mb; p = .001 and DPA 1.4 mut/Mb; p = .003). PD-L1 expression was not significantly different in all the MCADCA with low positive scores SWT vs SEB (37.0% vs 33.3%; NS). **Conclusions:** As there is limited evidence on the treatment of MCADCA, we provide a repertoire of common GA found. An increased frequency of GA is observed in SEB MCADCA. Clinical trials are needed to evaluate MCADCA-based biomarkers prognostic of ICI response. Only then can we successfully incorporate novel therapeutic strategies in the evolving landscape of treatment. Research Sponsor: None.

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9588 **Poster Session**

A phase Ib study of endogenous T cell therapy using SLC45A2-specific CD8 T cells for patients with metastatic uveal melanoma.

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Background: Overall survival (OS) for patients (pts) with advanced uveal melanoma (UM) is poor compared with outcomes in cutaneous melanoma. Roughly half of all pts with UM will develop distant metastatic disease despite effective treatment of the primary tumor. Antigen-specific endogenous T cells (ETC) can be expanded and infused successfully in pts with many different types of cancer. Our group has identified epitopes of SLC45A2, a melanosomal transport protein, which are highly expressed in UM and are present at low levels in normal melanocytes. *In vitro*, we showed that cytotoxic T cells against SLC45A2 were able to kill HLA-matched UM cell lines. *In vivo*, we hypothesize that infused ETC can traffic to tumor sites. **Methods:** Between 6/2017 and 12/2022, we conducted a single-center, IRB-approved, first-in-human phase 1b dose escalation study of ETC targeting SLC45A2 in pts with metastatic UM (NCT03068624). Eligible pts with metastatic UM who express HLA-A*02:01 or A*24:02 underwent apheresis to collect peripheral T cells which were then selected and expanded (Turnstile 1). For Turnstile 2, conditioning with low-dose cyclophosphamide (300 mg/m^2) occurred on Day -2. For pts in the radiation cohort, radiation occurred between Day -7 and Day -1. Infusion of ETC was done via hepatic arterial or central venous catheter on Day 0 followed by low dose subcutaneous interleukin-2 (IL-2) twice daily for 14 days +/- ipilimumab. The study utilized a 3+3 design with a starting dose level of 3.3 x 10^9 cells/m^2 of ETC alone. The primary objective was to evaluate the safety and tolerability of infusing ETC targeting SLC45A2. Secondary objectives were to evaluate the *in vivo* persistence and anti-tumor efficacy of this regimen. **Results:** With a median age of 58 years (30-77), 34 pts were enrolled, 16 (47%) men and 18 (53%) women. 33 (97%) pts underwent apheresis and 11 (32%) received infusion of ETC. One dose limiting toxicity (DLT) thought to be unrelated to treatment or underlying cancer (cardiac disorder Grade 5) occurred at the starting dose level with no additional DLTs. The maximum tolerated dose was established as 1 x 10^{10} cells/m^2. The most common treatment-related grade 3 and 4 toxicities were lymphocyte count decrease 9 (82%), hyponatremia 1 (9%), and hypophosphatemia 1 (9%). Per immune-related response criteria (irRC), 4 (36%) pts had stable disease (SD), 6 (55%) had progression of disease (PD), and 1 (9%) was not evaluable for best response. Median overall survival (OS) was 8.9 weeks (wks). OS was 91% at 4 wks, 55% at 8 wks and 46% at 13 wks. Median progression-free survival was 5.9 wks. In the 4 patients with stable disease, the median duration of SD was 5.7 months. **Conclusions:** ETC targeting SLC45A2 is safe and well-tolerated in pts with metastatic UM. Further analyses are underway to evaluate T cell trafficking and persistence. Clinical trial information: NCT03068624. Research Sponsor: U.S. National Institutes of Health; Cancer Prevention and Research Institute of Texas CPRIT: RP170317.

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9589 **Poster Session**

Early ctDNA reduction may identify patients with stable disease and long OS on tebentafusp.

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Background: Tebentafusp, a bispecific (gp100 × CD3) ImmTAC showed significant overall survival (OS) benefit (HR 0.51) versus investigator's choice in a Phase (Ph) 3 trial in first line (1L) HLA-A*02:01+ adult patients (pts) with metastatic uveal melanoma (mUM) [Nathan NEJM 2021]. In Ph2 and Ph3 trials of tebentafusp, OS was improved regardless of RECIST best response and the degree of early reduction in ctDNA was a better predictor of OS [Carvajal Nat Med 2022; Sullivan AACR 2023]. Here we explored whether early on-treatment reduction in ctDNA could distinguish pts with stable disease (SD) and long OS vs those with SD and short OS in a Ph3 trial of tebentafusp in 1L mUM pts. **Methods:** 1L HLA-A*02:01+ pts with mUM received 68 mcg tebentafusp weekly intravenously after intra-patient dose escalation (NCT03070392). Response was assessed by investigators per RECISTv1.1. Sera collected at baseline (BL) and week 9 on tebentafusp were analyzed for ctDNA using targeted mPCR-NGS assay for mutations in 15 genes including GNAQ, GNA11, SF3B1, CYSLTR2, PLCB4 and EIF1AX. Landmark OS from week 9 was analyzed in subsets with ≥0-3 log reductions in mean tumor molecules (MTM) per ml of serum on treatment. Data cutoff 11-Nov-2022. **Results:** 76/245 (36%) tebentafusp-treated pts had best response of SD, with a median OS of 29 months and were evaluable for ctDNA. Baseline tumor burden as assessed by sum of longest lesion diameters and percentage of pts with elevated BL serum LDH were greater in the subset with < 1 year (yr) OS (median 70 mm and 64%, respectively) than in subsets with OS ≥ 1 yr (median 42 mm, 11%) or OS ≥ 2 yrs (median 31 mm, 9%). Almost half (36/76; 47%) of all SD pts had detectable ctDNA mutations in one or more UM genes at baseline. Baseline ctDNA levels were similar across survival groups. By week 9 on-treatment, ctDNA reduction was observed in 34/36 (94%) evaluable SD pts, including 29/36 (81%) with ≥ 0.5 log reduction, 18/36 (50%) with ≥ 2 log reduction and 16/36 (44%) with undetectable ctDNA (clearance). Deeper reductions in ctDNA were associated with better OS (Table). **Conclusions:** In this Ph3 trial, ctDNA reduction by week 9 on tebentafusp was strongly associated with improved OS in pts with best RECIST SD. Early ctDNA reduction may predict SD patients with long OS on tebentafusp. Research Sponsor: Immunocore.

ctDNA subset	N (%)	OS hazard ratio (95% CI)*	≥ 1-year OS %	≥ 2 year OS %
All stable disease with evaluable ctDNA	76 (100%)	NA	73%	51%
ctDNA detected at baseline	36/76 (47%)	NA	78%	48%
ctDNA not detected at baseline	40/76 (53%)	NA	90%	72%
No decrease by week 9	2/36 (6%)	NA	50%	50%
Any (>0 log) decrease by week 9	34/36 (94%)	1.02 (0.14-7.67)	79%	48%
≥0.5 log	29/36 (81%)	0.61 (0.23-1.64)	83%	53%
≥2 log	18/36 (50%)	0.33 (0.14-0.78)	89%	72%
≥3 log (ctDNA clearance)	16/36 (44%)	0.28 (0.12-0.67)	94%	75%

*HRs estimated from Kaplan-Meier analysis for subsets above vs below ctDNA reduction threshold.

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9590 **Poster Session**

Survival outcomes associated with liver-directed therapies in patients with metastatic uveal melanoma.

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Background: Metastatic uveal melanoma (mUM) is characterized by a hepatotropic pattern of spread and poor outcomes. Tebentafusp, the only FDA approved therapy, is restricted to patients (pts) with the HLA-A*02:01 genotype. As a result, a variety of liver-directed therapies (LDT) are commonly used for management of hepatic metastases. **Methods:** Pts with mUM with hepatic metastases who underwent LDT, including radiofrequency ablation, microwave ablation, hepatic metastatectomy, Yttrium-90 radioembolization (SIRT), transarterial chemoembolization (TACE), bland embolization, and immunoembolization (IE), were identified from an institutional database. Data collected included: age, gender, tumor location and size, baseline liver function tests (LFT) and lactate dehydrogenase (LDH), molecular tumor characteristics (where available), type(s) of LDT received, systemic therapies received, and vital status. Time from onset of hepatic metastasis until death (Liver-OS), as well as time from initial diagnosis of primary uveal melanoma until death (Ocular-OS) were calculated. **Results:** A total of 119 pts were identified. The median age at diagnosis was 53.8 years (range 26-83), 47% were female. At the time of LDT initiation, 33% had bilobar disease and 16% had extrahepatic metastasis. 18% pts had elevated LFTs and 55% had elevated LDH. 72% of pts had M1a disease, 24% had M1b and 4% had M1c disease. 45% of pts received more than one form of LDT. SIRT (31%) was the commonly administered initial LDT, followed closely by IE (26%) and TACE (9%). 86% of pts received systemic therapy including 42% who received immune checkpoint blockade overlapping with LDT. Molecular profiling in 26 pts revealed recurrent mutations in BAP1 (n = 18) and SF3B1 (n = 8). The median ocular-OS across all pts was 71.0 months (95% confidence intervals (CI), 62.8-99.4). The median liver-OS across all pts was 31.8 months (95% CI 25.2-35.3). In pts who received TACE, IE, or SIRT exclusively (n = 44), the median Liver-OS was 15.2 months (95% CI 12.8-NA) for TACE (n = 8), 23.3 months (95% CI 15.8-NA) for SIRT (n = 28), and 28.2 months (95% CI 22.6-NA) for IE (n = 8). **Conclusions:** Our results provide additional support for the utilization of LDT in pts with mUM, as demonstrated by improved OS compared to historical survival data. Research Sponsor: None.

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9591 **Poster Session**

Long-term outcomes of chronic immune-related adverse events from adjuvant anti-PD-1 therapy for high-risk resected melanoma.

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Background: Adjuvant anti-PD1 improves relapse-free survival in high-risk, resected melanoma, but can lead to irAEs, which become chronic in up to 41% of patients (Patrinely et al, JAMA Onc 2021). Given the expanding use of anti-PD-1 in earlier settings in many tumors, it is imperative to assess their long-term effects. We aimed to determine the incidence, characteristics, and long-term outcomes, including resolution vs persistence, of chronic irAEs from adjuvant anti-PD1. **Methods:** We retrospectively analyzed patients (pts) treated with adjuvant anti-PD1 for resected stage III-IV melanoma from 2015-2022 from 6 institutions; all pts had at least 18 month follow up post-anti-PD1 discontinuation. Demographics, disease characteristics, treatment and recurrence details, and outcomes were collected. Type, grade, duration, treatment, and resolution of acute (onset during treatment) and chronic irAEs (defined as those extending 6+ months after treatment cessation) were characterized. **Results:** Among 318 pts, 226 (64%) developed acute irAEs arising during treatment, including 44 (20%) with grade 3-5 irAEs. Chronic irAEs developed in 147 (46%) pts, of which 74 (50%) were grade 2+, 6 (4%) were grade 3-5, and 100 (68%) were symptomatic. With long-term follow-up (median 35 months), 52 (35%) pts experienced resolution of chronic irAEs while 95 (30% of the full cohort) had persistent chronic irAEs at last follow-up. Among these 95 pts with persistent chronic irAEs, 43 (45%) were grade 2+, 42 (44%) were symptomatic, 24 (16%) were on steroids, and 42 (29%) were on other management. The most common persistent chronic irAEs were hypothyroid (n = 38), arthritis (n = 18), dermatitis (n = 9), and adrenal insufficiency (n = 8). Of 37 pts with chronic irAEs who received additional immunotherapy, 12 (32%) had a flare, 10 (27%) had no effect, and 20 (54%) had a distinct irAE. **Conclusions:** In this large cohort of anti-PD1 treated pts, chronic irAEs were common (46%) and frequently were persistent with long-term follow up (30%, most often hypothyroid and arthritis). Prolonged monitoring and management are needed for these long-term survivors. Research Sponsor: Burroughs Wellcome Fund; Susan and Luke Simons Directorship for Melanoma, the James C. Bradford Melanoma Fund, the Van Stephenson Melanoma Fund; U.S. National Institutes of Health.

N (% of pts with chronic irAEs)		
Any chronic irAE	147	
Resolved	52 (35)	
IrAE	**N (% of total pts)**	**Ongoing at last follow up (> 1.5 years) (% of pts with chronic irAE)**
Adrenal insufficiency	8 (3)	8 (100)
Arthritis	26 (8)	18 (69)
Dermatitis	21 (7)	9 (43)
Xerostomia	10 (3)	6 (60)
Hypophysitis	8 (3)	8 (100)
Pneumonitis	8 (3)	3 (38)
Hypothyroid	48 (15)	38 (79)

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TPS9592 **Poster Session**

ARTISTRY-6: Nemvaleukin alfa monotherapy in patients with advanced mucosal and cutaneous melanoma.

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Background: Despite improved outcomes in melanoma with the introduction of checkpoint inhibitors (CPIs), ≈50% of patients do not respond. A subset of responders ultimately progress and have limited treatment options, underscoring a high unmet need for novel treatments with durable benefit. Patients with mucosal melanoma exhibit response rates and progression-free survival ≈2 times lower than those with cutaneous melanoma. Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds to the intermediate-affinity interleukin-2 receptor complex to preferentially activate $CD8^+$ T and natural killer cells, with minimal expansion of regulatory T cells. Nemvaleukin has been granted Orphan Drug designation for the treatment of mucosal melanoma by the US FDA. In the ARTISTRY-1 study, the intravenous (IV) recommended phase 2 dose (RP2D) for nemvaleukin monotherapy (6 μg/kg on days 1-5 of a 21-day cycle) demonstrated durable antitumor activity in patients with advanced melanoma, including mucosal melanoma, previously treated with a CPI (N = 46, overall response rate [ORR] 13.0% [95% CI 4.9-26.3], median duration of response 8.1 weeks [range 6.1-79.0]). In the ARTISTRY-2 study, the subcutaneous (SC) RP2D was identified as 3 mg every 7 days, which demonstrated pharmacodynamic effects consistent with those of IV delivery. Data from these studies support further evaluation of nemvaleukin monotherapy among patients with advanced mucosal or cutaneous melanoma. Additionally, a less frequent IV nemvaleukin dosing schedule is being evaluated in patients with advanced solid tumors in the ARTISTRY-3 study. **Methods:** ARTISTRY-6 (NCT04830124) is an ongoing phase 2, global, multicenter, open-label study that is currently enrolling. Eligible patients will have had prior anti–PD-(L)1 therapy with or without anti–CTLA-4 therapy, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic reserve and hepatic and renal function. In Cohort 1, patients with advanced cutaneous melanoma will receive nemvaleukin at the SC RP2D of 3 mg every 7 days. In Cohort 2, patients with advanced mucosal melanoma will receive nemvaleukin at the IV RP2D of 6 μg/kg on days 1-5 of a 21-day cycle. In Cohort 3 (added as a protocol amendment), patients with advanced cutaneous melanoma will receive IV nemvaleukin in 1 of 2 less frequent dosing schedules of 1 or 2 doses per cycle. The dosing schedules for Cohort 3 will be determined when a less frequent IV RP2D has been established in ARTISTRY-3. Patients will receive nemvaleukin until progression or intolerable toxicity. The primary objective is to evaluate the antitumor activity of nemvaleukin monotherapy defined by ORR. Additional objectives include evaluation of safety, health-related quality of life, predictive biomarkers, pharmacokinetics, immunogenicity, and pharmacodynamic effects. Clinical trial information: NCT04830124. Research Sponsor: Alkermes, Inc.

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TPS9593 **Poster Session**

Camrelizumab combined with anlotinib and nab-paclitaxel in patients with untreated advanced mucosal melanoma: A single-arm, multicenter, exploratory study.

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Background: Anti-programed cell death-1 (PD-1) monotherapy is a part of the standard treatment for cutaneous melanoma, but its efficacy in mucosal melanoma is not ideal. In vivo studies have demonstrated that co-inhibition of the VEGF receptor (VEGFR) and PD-1 pathways increased T cell infiltration and suppressed tumor growth synergistically. Early phase trial data confirmed that PD-1 inhibitors combined with anti-angiogenic drugs showed efficacy in the treatment of advanced mucosal melanoma, but still did not meet clinical needs. Previous studies have shown that chemotherapy combined with anti-angiogenic drugs has significantly improved median PFS and median OS compared with chemotherapy alone, and has a certain effect as a salvage treatment for progression after PD-1 inhibitor treatment. In addition, previous retrospective analysis showed that PD-1 inhibitors combined with chemotherapy drugs such as nab-paclitaxel were superior to anti-PD-1 monotherapy in the treatment of advanced mucosal melanoma. In summary, the combination of anti-PD-1, anti-angiogenic drugs and chemotherapy may bring new hope for the treatment of advanced mucosal melanoma. **Methods:** This is a single-arm, multicenter, exploratory study to evaluate the efficacy and safety of camrelizumab combined with anlotinib and nab-paclitaxel as first-line therapy in patients with advanced mucosal melanoma. The trial is expected to enrol 66 patients. Key Inclusion Criteria are pts with confirmed recurrence, unresectable or metastatic mucosal melanoma after surgery (stage III/IV) and ECOG performance status of $\leq$1.Pts with previous adjuvant therapy or neoadjuvant therapy (except PD-1/PDL1 monoclonal antibody and VEGFR TKI) at least 4 weeks before the first administration of the study drug are allowed. Patients received intravenous camrelizumab (200 mg) on day 1, intravenous nab-paclitaxel (260mg/m^2) on day 1, and oral anlotinib (8mg) on days 1-14 every 3 weeks. The primary endpoint is objective response rate (ORR). Secondary endpoints include disease control rate (DCR),progression-free survival (PFS), and 2-year overall survival (OS). Clinical trial information: NCT04979585. Research Sponsor: Jiangsu Hengrui Medicine Co.,Ltd.

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TPS9594 **Poster Session**

A phase 2/3 trial in progress on tebentafusp as monotherapy and in combination with pembrolizumab in HLA-A*02:01+ patients with previously treated advanced non-uveal melanoma (TEBE-AM).

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Background: Tebentafusp is a bispecific (gp100 x CD3) ImmTAC that can redirect T cells to target gp100+ melanoma cells. In a Phase (Ph) 3 trial, tebentafusp demonstrated an overall survival (OS) benefit (HR 0.51) compared to investigator's choice (IC) in first line HLA-A*02:01+ patients with metastatic uveal melanoma (mUM). Gp100, which has limited expression in normal cells, is overexpressed in melanoma, including skin melanoma, supporting the investigation of tebentafusp in non-uveal melanoma. In a first-in-human trial, tebentafusp monotherapy demonstrated a promising 1-year OS (~74%) in anti-PD(L)1 naïve HLA-A*02:01+ patients with metastatic cutaneous melanoma (mCM). In a subsequent Ph1 trial, tebentafusp combined with anti-PDL1, with or without anti-CTLA4, demonstrated a 1-year OS of 75% in patients with mCM who progressed on prior anti-PD(L)1 therapy, which compares favorably with recent benchmarks (1-year OS 38%-57%) in similar patient populations.[1-3] The promising activity of tebentafusp as monotherapy and in combination with anti-PD(L)1 agents in advanced melanoma (AM) provides the rationale to conduct a Ph2/3 trial of tebentafusp (TEBE-AM; NCT05549297) in patients who have progressed on standard of care therapies. In mUM trials, RECIST response underestimated the OS benefit of tebentafusp, whereas a strong association was shown between OS and early reduction in ctDNA levels relative to baseline.[4] As an early measure of changes in tumor burden, ctDNA reduction is included as an innovative dual primary endpoint with OS for the Ph2 part of this study. **Methods:** TEBE-AM is a multicenter, open-label, seamless Ph2/3 study in HLA-A*02:01+ patients with non-uveal AM who have progressed on prior anti-PD(L)1, received prior ipilimumab, and a prior BRAF/MEK inhibitor regimen if actionable *BRAF* mutation is present. Patients are randomly assigned (1:1:1) to receive tebentafusp monotherapy, tebentafusp combined with pembrolizumab, or IC. In the IC arm, patients may enroll in clinical trials of investigational agents, receive local standard of care, or receive best supportive care, while being followed for key endpoints. Randomization into the Ph3 portion will commence immediately following completion of accrual into the Ph2 portion. Efficacy from the Ph2 portion may inform changes to the Ph3 design. Primary endpoints are ctDNA reduction relative to baseline and OS in Ph2 and OS in Ph3. Ph2 enrollment opened in Jan 2023 in the US and is expected to open in other countries mid-2023. Clinical trial registration: NCT05549297. 1. Zimmer L, et al. Eur J Cancer 75:47–55, 2017. 2. Silva IPD, et al. J Clin Oncol 38:10005–10005, 2020. 3. Arance AM, et al. J Clin Oncol 39:S9504, 2021. 4. Carvajal RD, et al. Nat Med 28:2364-2373, 2022. Clinical trial information: NCT05549297. Research Sponsor: Immunocore.

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TPS9595 **Poster Session**

Phase Ib/II study of XmAb23104 (PD1 X ICOS) and XmAb22841 (CTLA-4 X LAG3) combination in metastatic melanoma refractory to prior immune checkpoint inhibitor therapy with and without CNS disease.

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Background: Immune checkpoint inhibitors (ICI) have greatly improved outcomes for patients by targeting programmed cell death protein 1 (PD1), cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) and Lymphocyte Activation Gene-3 (LAG-3) to increase immune-mediated anti-tumor response. Despite these advances, ~50% of patients with metastatic melanoma do not respond to standard of care ICI. We strive to address this unmet clinical need through a Phase Ib/II, first-in-human, multi-center trial of two bispecific antibodies targeting four different immune checkpoints: XmAb23104 (PD1 X ICOS) and XmAb22841 (CTLA-4 X LAG3) in patients with melanoma refractory to ICI. This is the first trial of quadruple checkpoint inhibitor therapy. Furthermore, bispecific antibodies may allow simultaneous checkpoint blockade on the same cell and have been shown to heighten T cell activation in pre-clinical models. Two ongoing phase I trials of these bispecific antibodies with PD1 therapy have observed an immune related adverse event (irAE) rate of 20-24% with efficacy analysis ongoing (NCT03752398; NCT03849469). We postulate that treatment with XmAb23104 and XmAb22841 will enhance immune activation, overcome resistance, and improve disease control for patients refractory to traditional ICI. **Methods:** Eligible patients must have advanced/metastatic melanoma and have progressed on prior PD1/PD-L1 inhibitor or PD1/CTLA4 dual inhibition. Cutaneous, acral, mucosal and melanoma of unknown origin are allowed. Patient with CNS metastasis are allowed if these are asymptomatic and stable on MRI imaging obtained within 4 weeks of enrollment. Patients with prior unresolved irAE or irAE $\geq$ grade 3 are not allowed. XmAb23104 and XmAb22841 will be given on D1 and D15 of a 28-day cycle for 4 cycles, after which XmAb23104 (PD1 X ICOS) will be given alone for a total of 2 years. The phase I portion will be a dose escalation using standard 3+3 design of XmAb22841 (CTLA-4 X LAG3) with three dose levels (0.3 mg/kg, 1 mg/kg and 3 mg/kg). The dose of XmAb23104 (PD1 X ICOS) will remain at 10 mg/kg. These doses were selected based on results of prior early phase trials when these agents were combined with PD1. Once the P2RD of XmAb22841 (CTLA-4 X LAG3) is established, we will move on to dose escalation using a Simon's 2-stage design. This portion will include two arms: Arm A consisting of 17 patients without CNS disease and Arm B consisting of 17 patients with CNS disease (total 34). Primary endpoints include dose limiting toxicities (DLT)/irAE and Objective Response Rate (ORR) at the time of best response by RECIST 1.1. Secondary endpoints include progression-free survival, overall survival, CNS response. At the time of this abstract submission, Cohort 1 of dose escalation has begun with the first few patients still within the DLT observation window. Clinical trial information: NCT05695898. Research Sponsor: Xencor.

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TPS9596 **Poster Session**

Phase II study of niraparib in patients with advanced melanoma with genetic homologous recombination (HR) mutation/alteration.

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Background: There are a limited number of therapeutic options available for metastatic melanoma patients progressing on the checkpoint inhibitor(s) and BRAF-targeting drugs. PARP inhibitors have been approved in the setting of BRCA1/2 germline mutations, and have demonstrated activity in the setting of HR deficiency in other cancers. Documentation of PARP inhibitors in melanoma would have clear clinical impact. We have previously shown that 21-34% of metastatic melanomas harbor at least 1 molecular aberration in the HR pathway, considered pathogenic, and likely leading to HR deficiency. Previously, we demonstrated dramatic regression of tumors harboring HR mutation(s) with PARP inhibitor treatment in a PDX model. These findings provide a strong rationale to evaluate the clinical efficacy of a PARP inhibitor in patients with advanced melanoma with HR deficiency. **Methods:** This is a single arm, open-label, multi-center phase II trial. The primary objective of the study is: To evaluate the clinical efficacy of niraparib in advanced melanoma patients with HR deficiency. The secondary objectives is to evaluate PFS, OS, and safety profile of niraparib. The key eligibility criteria: Advanced melanoma patients with mutation in any of the following: ARID1A/B, ARID2, ATM, ATR, ATRX, BARD1, BRCA1/2, BAP1, BRIP1, CHEK2, FANCD2, MRN11A, RAD50, RAD51, RAD54B, PALB2 (requires a genetic analysis result performed at any CLIA-certified laboratory) disease progression on PD1-antibody therapy and if BRAF mutant, BRAF/MEK inhibitors $\geq$ 18 years of age; ECOG PS $\leq$ 1; prior systemic cytotoxic therapy $\leq$1 regimen; no limit on number of prior immunotherapy or targeted therapy regimens. No symptomatic brain metastasis; active brain lesions $\geq$6 mm size, or requiring steroid treatment Patients will be treated with oral niraparib once daily (28-day cycle); the dose will be 300 mg (if weight $\geq$77 kg and platelet counts of $\geq$150,000 μL); otherwise 200 mg RECIST 1.1 will be used to evaluate clinical response every 8 weeks. Adverse events will be recorded according to CTCAE version 4.03. The primary study endpoint is overall response rate. Simon's optimal 2-stage design is proposed. With significance level of5% and 80% power, our null hypothesis that the true response rate is 0.10 will be tested against a one-sided alternative: H0: p $\leq$ 10%, a response rate of no real interest VS H1: p $\geq$ 30%, a response rate that would be of considerable interest 10 patients will be analyzed for a response evaluation in the first stage of the study, and 19 in the second stage, for a total of 29 patients. If the response rate is 10% (1/10) or less at the end of the first stage, further accrual will be terminated. With 2 or more responses in the first stage, accrual will continue to a total of 29 patients for this cohort. The null hypothesis will be rejected if $\geq$6 responses are observed in a cohort of 29 subjects. Clinical trial information: NCT03925350. Research Sponsor: Glaxo Smith Kline.

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TPS9597 **Poster Session**

Phase 1 study of SGN-BB228, an investigational CD228 x 4-1BB costimulatory antibody anticalin bispecific, in patients with advanced melanoma and other solid tumors (SGNBB228-001).

Jason Timothy Henry, Janice M. Mehnert, Erika Rudnicki, Juan Pinelli, Adil Daud; Sarah Cannon Research Institute at HealthONE, Denver, CO; New York University Langone Health, New York, NY; Seagen, Inc., Bothell, WA; University of California, San Francisco, San Francisco, CA

Background: SGN-BB228 is an investigational costimulatory Antibody Anticalin bispecific (Mabcalin) molecule directed to CD228 and 4-1BB. CD228 is a tumor-associated antigen selectively expressed by multiple tumor types including melanoma, mesothelioma, pancreatic, colorectal, and lung cancers with minimal expression in normal tissue. 4-1BB is an inducible costimulatory receptor expressed on activated T cells and other immune cell populations. The clinical development of 4-1BB agonist antibodies has been hampered by limited efficacy and/or poor tolerability at active doses (Segal et al 2017, Segal et al 2018). SGN-BB228 is designed to deliver a potent costimulatory bridge between tumor-specific T cells and tumor cells, potentially localizing antitumor activity to the tumor microenvironment and expanding the therapeutic window for 4-1BB agonism. In vitro, SGN-BB228 shows potent CD228-conditional 4-1BB stimulation and cytotoxic T cell activation (Updegraff et al 2022) providing rationale for evaluating SGN-BB228 in patients (pts) with melanoma or other solid tumors.
Methods: SGNBB228-001 (NCT05571839) is a phase 1, open label, multicenter study designed to evaluate the safety, tolerability, PK, and antitumor activity of SGN-BB228 in adults $\geq$18 years of age with advanced melanoma or other solid tumors. The study includes dose escalation (Part A), dose and schedule optimization (Part B; optional), and dose expansion in disease-specific cohorts (Part C). Parts A and B will enroll pts with histologically or cytologically confirmed metastatic or unresectable cutaneous melanoma, and Part C will enroll pts with cutaneous melanoma, mesothelioma, pancreatic, colorectal, or non-small cell lung cancer. Pts must have disease that is relapsed, refractory, or intolerant to standard of care therapies, ECOG PS 0-1, and adequate organ function. Pts with known active CNS metastases or prior use of agents targeting CD228 or 4-1BB are excluded. Pts with cutaneous melanoma must have received anti PD(L)-1 agent as monotherapy or in combination. Pts with a targetable BRAF mutation must have received, been intolerant to, or declined treatment with BRAF/MEK targeted therapy prior to study entry. Primary endpoints include rate of adverse events, laboratory abnormalities, dose-limiting toxicities, and cumulative dose-level safety. Secondary endpoints are PK, ORR, DOR, PFS, OS, and incidence of antidrug antibodies. Safety and antitumor activity endpoints will be assessed by dose, schedule, and tumor type using descriptive statistics. The ORR and its 95% CI will be estimated. DOR, PFS, and OS will be estimated using Kaplan-Meier method. Enrollment is ongoing in the US and planned in Europe. Clinical trial information: NCT05571839. Research Sponsor: Seagen Inc.

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TPS9598 **Poster Session**

A phase 3 trial comparing fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) to pembrolizumab in patients with completely resected high-risk melanoma.

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Background: Melanoma (Mel) accounts for the majority of skin cancer-related deaths. Most patients (pts) with a newly diagnosed Mel have resectable disease and are potentially cured by surgery. However, regional nodal and/or distant relapses can occur after curative-intent resection. Postoperative adjuvant therapy with immune checkpoint inhibitors improves relapse-free survival (RFS) and distant metastasis-free survival (DMFS) of pts at high risk of Mel. Fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) are both high-affinity, fully human, IgG4 monoclonal antibodies (MAbs) that combined have shown high clinical activity in pts with advanced Mel in a phase 1 study. Additionally, combination of relatlimab (anti-LAG-3) and nivolumab (anti-PD-1) have shown superiority over nivolumab for PFS in advanced Mel. These observations provide a rationale for use of fianlimab and cemiplimab combination in high-risk adjuvant Mel. **Methods:** Our study (NCT05608291) is a three-way, double-blind, phase 3 trial to compare fianlimab + cemiplimab to pembrolizumab in the adjuvant therapy (Rx) of high-risk, resected Mel. The primary objective is RFS, and the secondary objectives are overall survival, safety, pharmacology, and immunogenicity. This international trial will be conducted at 200 sites. Pt eligibilities: (1) $\geq$12 years of age; (2) Stage IIc, III or IV (all M-stages) and histologically confirmed Mel, completely resected $\leq$12 weeks prior to randomization; (3) no prior systemic anti-cancer Rx or radiation Rx for Mel in the previous 5 years; (4) no evidence of metastatic disease on staging investigations; and (5) an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 (for adult pts), Karnofsky PS $>$70 (pts $>$16 years) or Lansky PS $>$70 (pts $<$16 years). Study arms (all Rx every 3 weeks intravenously for one year): A. fianlimab (1600 mg) + cemiplimab (350 mg); B. fianlimab (400 mg) + cemiplimab (350 mg); C. pembrolizumab (200 mg) + saline/dextrose placebo. The placebo controlled trial will enroll about 1530 pts, randomized 1:1:1 to Arms A:B:C, treated for up to 1 year. The trial will stratify by disease stage (stage IIIA vs IIC-IIIB-IIIC vs IIID-IV [M1a/b] vs IV [M1c/d]), and geography (North America vs Europe vs Rest of World). The primary endpoint is investigator-assessed RFS. The secondary endpoints include efficacy (overall survival, DMFS, melanoma-specific survival), safety [treatment-emergent adverse events (TEAEs), interruption or discontinuation of drugs due to TEAEs], pharmacokinetic (concentrations of fianlimab and cemiplimab in serum over time), immunogenicity (anti-drug Abs and neutralizing Abs in serum against fianlimab or cemiplimab), and patient reported outcomes. The first analysis will be performed when 242 RFS events have been observed. Clinical trial information: NCT05608291. Research Sponsor: Regeneron Pharmaceuticals, Inc.

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TPS9599 **Poster Session**

OMNIA-1: A phase I/II study, an IL-2R-βγ targeted antibody-IL-2 fusion protein, as monotherapy or in combination with anti-PD-1 or anti-CTLA-4 antibodies, in patients with advanced melanoma.

Paolo Antonio Ascierto, Guillermo de Velasco, Thomas Eigentler, Nicolas Isambert, Julie Mouton, Caroline Robert, Claudia Michaela Schusterbauer, Jayanthi Vijayakumar; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; Charite-Universitaetsmedizin, Berlin, Germany, Berlin, Germany; CHU, Poitiers, France; ANAVEON AG, Basel, Switzerland; Gustave Roussy and Paris-Saclay University, Villejuif, France; Anaveon, Basel, Switzerland; Health Partners Institute, Minneapolis, MN

Background: ANV419 is a potent and selective IL-2Rβγ targeted antibody IL-2 fusion protein, designed to enable the delivery of high dose interleukin-2 (IL-2) to patients in order to stimulate anti-tumour response and minimise toxicities. Recombinant IL-2 (proleukin) induces durable responses in approximately 10% of patients with melanoma. Signalling through IL-2Rα expressing cells is believed to limit its therapeutic potential in cancer. By eliminating binding to IL-2Rα, ANV419 could lead to increased anti-tumor effect while increasing tolerability. The ANV419-001 first-in-human study (NCT 04855929) demonstrated that ANV419 preferentially stimulates cytotoxic CD8+ T and natural killer (NK) cells over immunosuppressive regulatory T cells, with a significantly longer half-life than that of conventional IL-2. The safety and tolerability data from this study confirmed that ANV419 delivers high molar equivalents of IL-2 in a tolerable and convenient way. **Methods:** ANV419 is being evaluated in a global multicentre, open-label, randomized Phase I/II study in patients with unresectable or metastatic cutaneous melanoma to assess the safety and efficacy of intravenous ANV419 as monotherapy and in combination with anti-PD1 or anti-CTLA-4 antibodies. The OMNIA-1 study leads in with a monotherapy dose expansion part, followed by a combination dose-finding with either anti-PD-1 or anti-CTLA-4 and a combination dose expansion part. ANV419 is administered intravenously every 2 weeks as monotherapy and every 3 weeks when given in combination. Patients with advanced cutaneous melanoma, no active brain metastases and whose disease has progressed on or following at least 1 line of standard of care immunotherapy are eligible. In Part 1, a total of 30 patients will be randomised and evaluated for response to Q2W ANV419 monotherapy (108 μg/kg or 243 μg/kg). In Part 2, escalating doses of Q3W ANV419 are evaluated to define the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) in combination with pembrolizumab (200 mg) or ipilimumab (3 mg/kg). In Part 3, the efficacy and safety of ANV419 in combination with the approved doses pembrolizumab or ipilimumab will be evaluated using a Simon's 2-stage design. Up to 130 patients are planned to be enrolled. Patients will be stratified according to BRAF mutation status. AEs are assessed according to CTCAE V5.0. Tumour response is determined using RECIST 1.1 criteria. The study is conducted at sites in the US, France, Spain, Germany, Italy, and UK. The first patient was dosed in December 2022. Preliminary monotherapy efficacy data are expected by Q1/2024. Clinical trial information: NCT05578872. Research Sponsor: Anaveon.

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TPS9600 **Poster Session**

NOTOS: A pivotal study of navtemadlin, a first-in-class mouse double minute 2 inhibitor (MDM2i), in patients (pts) with *TP53* wild-type (*TP53^{WT}*) Merkel cell carcinoma (MCC) for whom anti PD-1/L1 therapy has failed.

Michael K.K. Wong, Melissa Amber Burgess, Sunandana Chandra, Leslie Anne Fecher, Caroline Gaudy-Marqueste, Ann W. Silk, Glenn J. Hanna, Celeste Lebbe, Gaëlle Quéreux, Guilherme Rabinowits, Dirk Schadendorf, Caroline Dutriaux, Carola Berking, Juan Martin Liberal, Paolo Antonio Ascierto, Emily Houlihan, Kim Steinmann, Tiffanie Chan, Wayne P. Rothbaum, Ciara Marie Kelly; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Pittsburgh Medical Center, Pittsburgh, PA; Northwestern University, Chicago, IL; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; Aix-Marseille University, Marseille, France; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Université de Paris, AP-HP Hôpital Saint-Louis, Dermatology Department, Paris, France; University of Nantes, Nantes, France; Miami Cancer Institute, Miami, FL; University Hospital Essen, Essen, Germany; Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France; University of Erlangen, Erlangen, Germany; Catalan Institute of Oncology (ICO) Hospitalet, IDIBELL, Barcelona, Spain; Istituto Nazionale Tumori Istituto di Ricovero e Cura a Carattere Scientifico Fondazione Pascale, Naples, Italy; Kartos Therapeutics, Inc., Redwood City, CA; Memorial Sloan Kettering Cancer Center, New York, NY

Background: There are no approved therapies for pts with MCC for whom an anti PD-1/L1 agent has failed. The high rate of non-responsive disease after anti PD-1/L1 therapy together with high mortality rate and the absence of a standard of care in this setting highlight the urgent unmet need for effective novel therapies. Approximately 80% of MCC tumors carry the oncogenic Merkel cell polyoma virus (MCPyV) and most cases are *TP53^{WT}*. Oncoproteins from MCPyV inhibit p53 tumor suppressor functions by activating MDM2. Navtemadlin, a potent, selective, orally available MDM2i, overcomes MDM2 dysregulation by restoring p53 activity and inducing apoptosis of *TP53^{WT}* MCC tumors. Navtemadlin is the first targeted therapy to show single-agent activity in pts with metastatic MCC for whom anti-PD-1/L1 has failed (Wong ASCO 2022). In the dose finding study, evaluable pts (n=8) receiving the recommended phase 2 dose of navtemadlin (180 mg QD on Day 1-5/28-day cycle) demonstrated a 25% confirmed objective response rate (ORR), 38% unconfirmed + confirmed ORR, and 63% disease control rate. The median duration of response was not reached (range, 6-16.2+ months [mos]) and median time to treatment response was 4.1 mos (range, 1.2-7). Responses to navtemadlin were highest in those pts with no prior chemotherapy (chemo; Wong ASCO oral 2022). In pts receiving navtemadlin at doses of $\geq$180 mg, an ORR of 40% was reported with no prior chemo (n=15) versus 14% in those who received prior chemo (n=14, Wong ASCO oral 2022). Navtemadlin demonstrated an acceptable safety profile with the most common treatment emergent adverse events (TEAEs) cytopenias, nausea, vomiting, diarrhea, and fatigue. Grade 3/4 TEAEs were 32% anemia, 32% lymphopenia, and 19% thrombocytopenia (Wong 2022). Based on this encouraging data, the NOTOS study (navtemadlin induces p53-driven apoptosis in Merkel cell carcinoma) will evaluate the safety and efficacy of navtemadlin in two post PD-1/L1 treated cohorts: chemo-naive pts and chemo treated pts.
Methods: Adults with MCC for whom anti PD-1/L1 therapy has failed, who have $\geq$1 measurable lesion per RECIST v1.1, ECOG PS 0-1 and *TP53^{WT}* MCC by central testing will receive 180 mg QD on days 1-5 of a 28-day cycle until disease progression, unacceptable toxicity, death or withdrawal of consent. The primary endpoint is ORR per RECIST v1.1 by blinded independent review. Secondary endpoints include ORR per investigator, duration of response, progression-free survival, overall survival, clinical benefit rate (including stable disease for $\geq$10 wk, partial response or complete response), and safety. The NOTOS trial is currently enrolling (NCT03787602). Clinical trial information: NCT03787602. Research Sponsor: Kartos Therapeutics.

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TPS9601 **Poster Session**

Phase III study of adjuvant encorafenib plus binimetinib versus placebo in fully resected stage IIB/C BRAFV600-mutated melanoma: COLUMBUS-AD study design.

Alexander Christopher Jonathan Van Akkooi, Axel Hauschild, Georgina V. Long, Mario Mandalà, Michal Kicinski, Anne-Sophie Govaerts, Isabelle Klauck, Monia Ouali, Paul Lorigan, Alexander M. Eggermont; Melanoma Institute Australia, Wollstonecraft, Australia; University Hospital (UKSH), Campus Kiel, Department of Dermatology, Kiel, Germany; The University of Sydney, Sydney, NSW, Australia; University of Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy; European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium; European Organization for Research and Treatment of Cancer (EORTC), Headquarters, Brussels, Belgium; Pierre Fabre Medicament, Boulogne-Billancourt, France; Pierre Fabre Medicament, Boulogne Billancourt, France; The Christie NHS Foundation Trust, Manchester, United Kingdom; University Medical Center Utrecht & Princess Máxima Center, Utrecht, Netherlands

Background: Significant progress has been made in the treatment of advanced BRAFV600-mutant melanoma. Encorafenib in combination with binimetinib is a well-tolerated and effective treatment option, providing sustained progression-free and overall survival benefit in unresectable or metastatic setting. The focus has shifted to early-stage disease in order to prevent recurrence. 18% of stage IIB and 25% stage IIC patients die due to melanoma within 10 years from the diagnosis [Gershenwald and al 2017], indicating an unmet medical need. Currently only immunotherapy has been approved in first countries across the world in this setting. There is a need for more treatment options for *BRAF*-mutated stage II disease. We report here the rationale and design of COLUMBUS-AD (NCT05270044). **Methods:** COLUMBUS-AD study is an international randomized, placebo-controlled, triple-blind, multicenter Phase III trial evaluating adjuvant encorafenib + binimetinib against placebo in patients with fully resected stage IIB/C BRAF V600-mutant melanoma. Approximately 815 patients will be enrolled. More than 170 sites in up to 26 countries worldwide will participate in the study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC). Patients will receive encorafenib + binimetinib or placebo for 12 months, or until disease recurrence and will be followed monthly during treatment period, then every 3 months up to year 3, and then at regular intervals. The participants will be followed for a total of 10 years. Patients included in the study must have undergone resection of a stage IIB/C cutaneous melanoma with a BRAFV600E/K mutation, confirmed on resected tumor sample by a central laboratory, and a negative result on sentinel node biopsy. Patients must have recovered from surgery, have an ECOG 0/1, and adequate hematologic, hepatic, cardiac, coagulation and renal functions. Eligible patients will be randomized 1:1 to receive either encorafenib 450 mg once daily plus binimetinib 45 mg twice daily or matching placebos. The primary objective of the study is to evaluate the efficacy of the combination of encorafenib+ binimetinib for prolonging recurrence-free survival (RFS). The secondary objectives are to compare distant metastasis-free survival (DMFS), overall survival (OS), health-related quality of life (QoL), and safety and tolerability between the two arms and to provide additional pharmacokinetic data. Conclusion: COLUMBUS-AD is the first phase 3 randomised trial to evaluate adjuvant BRAFi/MEKi in stage IIB/C melanoma. This study will evaluate whether the combination of encorafenib and binimetinib can decrease the risk for recurrence and improve distant metastasis-free survival and overall survival versus placebo in completely resected IIB/C BRAFV600E/K-mutant cutaneous melanoma. Clinical trial information: NCT05270044. Research Sponsor: Pierre Fabre Medicament.

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TPS9602 **Poster Session**

A phase 3 trial of fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma.

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Background: Fianlimab (anti-lymphocyte activation gene 3 [LAG-3]) and cemiplimab (anti- programmed cell death-1 [PD-1]) are both high-affinity, fully human, IgG4 monoclonal antibodies (Abs). Concurrent blockade of anti-LAG-3 and anti-PD-1 has shown enhanced efficacy (increase in progression free survival [PFS]) in advanced melanoma (Mel). We previously presented data from a phase 1 study showing a 63.8% objective response rate (ORR) across two separate cohorts of advanced PD-(L)1 naïve metastatic Mel patients (pts) treated with fianlimab plus cemiplimab with an acceptable risk-benefit profile. **Methods:** This is a randomized, double-blind, phase 3 study to evaluate fianlimab plus cemiplimab compared to pembrolizumab in pts with previously untreated unresectable locally advanced or metastatic Mel (NCT05352672). This study will be conducted globally, at approximately 200 sites. Key inclusion criteria are: (1) $\geq$12 years of age; (2) histologically confirmed unresectable Stage III and Stage IV (metastatic) Mel (3) no prior systemic therapy for advanced unresectable disease, prior (neo)adjuvant therapies are allowed with treatment/disease-free interval of 6 months; (4) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; (5) valid LAG-3 results; (6) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 (for adult pts), Karnofsky PS $\geq$70 (pts $\geq$16 years) or Lansky PS $\geq$70 (pts $<$ 16 years); and (7) anticipated life expectancy of at least 3 months. There are 4 arms to the study: (1) Arm A: fianlimab (1600 mg) + cemiplimab (350 mg) every 3 weeks (Q3W), intravenously (IV); (2) Arm A1: fianlimab (400 mg) + cemiplimab (350 mg) Q3W, IV; (3) Arm B: pembrolizumab (200 mg Q3W, IV) + saline/dextrose placebo (placebo); (4) Arm C: cemiplimab (350 mg Q3W, IV) + placebo. The trial is expected to enroll approximately 1590 pts. The primary endpoint is progression-free survival. The key secondary endpoints are overall survival and objective response rate. The additional secondary endpoints include disease control rate, duration of response, safety, pharmacokinetics of cemiplimab and fianlimab, and immunogenicity (incidence and titer of anti-drug Abs and neutralizing Abs). The study is currently open for enrollment. Clinical trial information: NCT05352672. Research Sponsor: Regeneron Pharmaceuticals, Inc.

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TPS9603 **Poster Session**

A randomized phase 2 trial of encorafenib + binimetinib + nivolumab vs ipilimumab + nivolumab in BRAFV600-mutant melanoma brain metastases: SWOG S2000.

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Background: While anti-PD-1 and anti-CTLA4 immunotherapies are widely used in the treatment of metastatic melanoma, including melanoma brain metastases (MBM), their efficacy in patients with symptomatic MBM is very limited. In the Checkmate-204 trial of ipilimumab with nivolumab in MBM, the 6-month progression free survival (PFS) rate was 19% with a median PFS of only 1.2 months in symptomatic participants (those with neurological symptoms including steroids up to 4 mg/day of dexamethasone, n=18). (Tawbi, Lancet et al., 2021) In the COMBI-MB study of BRAF/MEK-inhibitors in BRAF-V600 mutant MBM, median PFS was 5.5 months in those with symptomatic metastases (n=17). (Davies et al., Lancet Oncol, 2017) The combination of anti-PD-1/PD-L1 therapy with BRAF/MEK inhibitors has been tested in various trials. The single-arm phase 2 TRICOTEL study explored the triplet regimen of vemurafenib + cobimetinib + atezolizumab in MBM; in the symptomatic brain met cohort, 6-month PFS was 57% (n=24). (Dummer et al., Lancet Oncol 2022). **Methods:** SWOG S2000 is a randomized phase 2 trial exploring the efficacy of a triplet regimen of BRAF/MEK inhibitors with PD-1 therapy (encorafenib 450 mg qday + binimetinib 30 mg BID + nivolumab 480 mg IV q4 weeks) versus ipilimumab 3 mg/kg + nivolumab 1 mg/kg q3 weeks in patients with symptomatic BRAF-mutant MBM. (The study was amended to exclude patients with asymptomatic MBM.) Eligible patients are $\geq$18 years old, ECOG 0-2, and prior neoadjuvant or adjuvant anti-PD-1, CTLA-4, or BRAF/MEK-inhibitors is permitted. Steroids up to 8 mg of dexamethasone/day (or equivalent), leptomeningeal spread, and prior local therapy (radiation or surgery) for brain mets are permitted, if a patient has at least one measurable, progressing brain met $\geq$0.5 cm in size. Primary objective is to compare PFS per (RECIST 1.1) between the two study arms. Secondary objectives include overall survival, toxicity profile, objective tumor response, intracranial response and duration per modified RECIST 1.1, modified RANO-BM, and iRANO criteria, and evaluation of radiographic response criteria by centralized review of banked images. This study is powered to detect an increase in estimated 6-month PFS from 20% to 52% with 80% power and type I error rate of 10%, with 24 eligible patients required. Total sample size is 28 to account for ineligible patients. Available blood, tissue, CSF and stool samples are banked for future correlative studies. The study is currently enrolling patients through SWOG, ECOG and NRG centers. Funding: NIH/NCI grants U10CA180888, U10CA180819, U10CA180820 U10CA180868; and in part by Pfizer, Inc. Clinical trial information: NCT04511013. Research Sponsor: U.S. National Institutes of Health.

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TPS9604 **Poster Session**

A pilot, open study to assess efficacy and safety of ON-01910 (rigosertib) in patients with recessive dystrophic epidermolysis bullosa associated locally advanced/metastatic squamous cell carcinoma.

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Background: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is an extremely rare, severe blistering disease driven by mutations in collagen seven (COL7A1). Besides the skin and mucosal blistering, this genodermatosis is also characterized by aggressive cutaneous squamous cell carcinomas (cSCCs) arising from patients' chronic wounds. The cumulative risk of death from these cSCCs is 70% by age 45. There are limited effective treatment options for advanced (unresectable/metastatic) RDEB-associated cSCCs. While the standard of care for any advanced cSCC is immune checkpoint inhibitors, only half of the treated patients had responses in clinical trials. Their use for RDEB-associated SCCs been limited to case reports, and our own experience has not been positive. Conventional chemotherapy in RDEB-associated cSCC is another proposed treatment strategy, however, case reports demonstrated limited response rates without lasting effects. Currently it is recommended palliatively, although there are concerns about adverse effects. Other existing options are tyrosine kinase inhibitors, resulting in mixed responses to treatment for advanced cSCCs of any type, and epidermal growth factor receptor inhibitors, demonstrating limited effectiveness in a small number of case reports on RDEB-associated cSCCs. More effective therapeutic modalities for advanced/metastatic RDEB-associated cSCCs are needed. We previously demonstrated that RDEB SCC keratinocytes are specifically affected by polo-like kinase-1 (PLK-1) siRNA. Eight PLK-1 inhibitors were screened for cytotoxicity. Of the 8 candidates, ON-01910 was superior as it demonstrated the largest therapeutic window for distinguishing between tumor versus normal cells. The ON-01910 clinical trial is in progress in patients with RDEB with advanced/metastatic cSCCs. **Methods:** ON-01910 is being evaluated in both oral and intravenous formulations in an open-label, non-randomized phase 2 study in RDEB patients with advanced, treatment resistant cSCC. The trial explores the anti-tumor activity of ON-01910 and evaluates its safety and tolerability. Secondary objectives are to assess the impact on quality of life and to perform biomarker analysis on patient tissue. This study began in August 2021 and is ongoing. One patient is currently enrolled in the oral arm at Thomas Jefferson University in the USA. Safety is assessed according to the CTCAE v5. Tumor response in lymph nodes is determined per the RECIST 1.1 and in skin via clinical examination with serial tumor measurements. Key eligibility criteria include 1) diagnosis of RDEB and associated measurable, advanced cSCC confirmed histologically 2) failure to respond to standard of care including excision for localized disease 3) no concomitant cancer therapies. Clinical trial information: NCT04177498. Research Sponsor: Dystrophic Epidermolysis Bullosa Research Association of America; Onconova Therapeutics.

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TPS9605 **Poster Session**

Phase II study of nivolumab (nivo) in combination with relatlimab (rela) in patients (pts) with active melanoma brain metastases (MBM).

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Background: More than half of all pts diagnosed with metastatic melanoma (MM) will develop brain metastases. Despite this prevalence, pts with MBM are excluded from the majority of clinical trials, preventing them from potential benefit of novel therapies. Long-term outcomes of the CheckMate 204 study combining ipilimumab (ipi) (3mg/kg) plus nivo (1 mg/kg) for asymptomatic MBM reported an intracranial (IC) response in 54% of pts. The 36-month IC progression-free survival (PFS) was 54% and overall survival (OS) was 72%. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 55% of pts. RELATIVITY-047, a global phase II/III randomized study, reported on the fixed-dose combination of nivo (480 mg) and rela (a LAG-3–blocking antibody,160 mg) compared to nivo (480 mg) alone for pts with advanced unresectable and untreated melanoma. The combination demonstrated significantly improved PFS and improved OS and objective response rate (ORR) compared to monotherapy. At 19.3 months of median follow-up, only the PFS benefit was statistically significant with a hazard ratio (HR) of 0.78 (95% CI 0.64-0.94). The OS benefit was not statistically significant (HR 0.8, 95% CI 0.64-1.01), and the descriptive ORR was 43.1% compared to 32.6% for single agent nivo. Grade 3 or 4 TRAEs occurred in 21% of pts in the combination group compared to 11% in the monotherapy group with no new safety signals. The nivo/rela combination has been FDA approved for the treatment of pts with MM but has not been studied in pts with MBM. We hypothesize that nivo/rela will be safe and tolerable for pts with MBM and demonstrate favorable outcomes compared to nivo monotherapy with fewer AEs in contrast to ipi/nivo combination. **Methods:** This single arm, single center, open-label phase II trial will evaluate the safety and efficacy of nivo/rela in pts with MBM (NCT05704647). 30 MBM pts who are treatment naïve to anti-PD-1 therapy will be enrolled. At least one unirradiated parenchymal brain metastasis at least 5 mm or larger is required for inclusion. Asymptomatic pts not requiring steroids for the management of their neurological symptoms are eligible. Pts requiring urgent local therapy with radiation or surgery are not eligible. Pts will be treated with nivo (480 mg)/rela (160 mg) every 4 weeks for up to 25 cycles, disease progression, or unacceptable toxicity. The primary objective is to evaluate IC ORR (CR + PR) by MRI per modified RECIST 1.1 criteria. Monitoring for futility will be performed using the Bayesian Optimal Phase 2 (BOP2) design. Thirty evaluable patients will provide 82% power to detect a difference between the historical IC ORR of 20% for nivo alone to a targeted ORR of 40% for nivo/rela. Longitudinal research blood, tissue, and microbiome samples will be collected along with neurocognitive assessment and quality of life surveys. Clinical trial information: NCT05704647. Research Sponsor: Bristol-Myers Squibb Company (BMS); MD Anderson Cancer Center Melanoma Moon Shots.

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TPS9606 **Poster Session**

A pilot trial of autologous tumor infiltrating lymphocytes (lifileucel, LN-144) for patients with asymptomatic melanoma brain metastases.

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Background: Melanoma brain metastases (MBM) are a leading cause of morbidity and mortality for patients with advanced melanoma. Modern systemic therapies are insufficient at controlling MBM, and median overall survival (OS) for pts with MBM is $<$ 1 year. Adoptive T cell therapy using tumor infiltrating lymphocytes (TIL) has demonstrated efficacy in advanced melanoma. Lifileucel (LN-144), an autologous TIL product, was recently shown to be safe and effective for patient with PD-1 refractory melanoma. Patients with active MBM were excluded from lifileucel trials to date. **Methods:** This single-center pilot trial (NCT05640193) is enrolling up to 10 pts with asymptomatic MBM from non-uveal melanoma to receive lifileucel. Patients must have $\geq$1 intracranial lesion measuring 5-30mm visible on MRI to be used as a target lesion for modified (m)RECIST measurement, progression on prior anti-PD-1 therapy (with or without anti-CTLA-4), progression on targeted therapy if BRAF V600E/K-mutated), ECOG PS $\leq$1, $\geq$1 resectable lesion(s) ($\geq$1.5 cm), recovered from prior surgery/anticancer treatment-related AEs (grade $\leq$1). Patients are not eligible if they have symptomatic MBM and/or require corticosteroids of $\geq$10 mg/day of prednisone or equivalent. Lifileucel is generated from resected tumor in a centralized GMP process. The regimen includes nonmyeloablative lymphodepletion, lifileucel infusion, and a short course of high-dose IL-2. The primary endpoint is feasibility, defined as $\geq$7/10 patients who undergo tumor harvest receiving lifileucel infusion. Secondary endpoints are safety, feasibility of manufacturing lifileucel in patients with MBM, and brain metastasis response rate (BMRR) per mRECIST 1.1. Exploratory endpoints include overall objective response rate by mRECIST 1.1, best extracranial response rate, intracranial progression-free survival (PFS), overall PFS, OS. Extensive correlative analyses of peripheral blood mononuclear cells, plasma, tumors, and cerebrospinal fluid are planned to better understand MBM growth, treatment resistance, and response of the central nervous system to lifileucel. Clinical trial information: NCT05640193. Research Sponsor: Iovance Biotherapeutics; Conquer Cancer Foundation of the American Society of Clinical Oncology; Melanoma Research Foundation; Memorial Sloan Kettering Cancer Center K12 Grant.

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TPS9607 **Poster Session**

A phase 3 study (TILVANCE-301) to assess the efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated unresectable or metastatic melanoma.

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Background: Most patients (pts) with advanced (unresectable or metastatic) melanoma receiving frontline immune checkpoint inhibitor (ICI) therapy progress within a year (Robert *Lancet Oncol* 2019; Larkin *NEJM* 2019; Tawbi *NEJM* 2022). Early-line therapies are needed to improve the rate of deep and durable responses and increase the proportion of pts with long-term benefit. Lifileucel demonstrated an ORR of 31.4% and median DOR not reached (median 36.5 mo follow-up) in pts with post-ICI advanced melanoma (Sarnaik *SITC* 2022). Earlier-line treatment with lifileucel plus pembrolizumab (pembro) in pts with ICI-naïve advanced melanoma demonstrated an ORR of 67%, including a CR rate of 25% (Iovance Press Release, April 5, 2022; O'Malley *JITC* 2021). TILVANCE-301 will evaluate the efficacy and safety of lifileucel plus pembro compared with pembro alone in pts with untreated advanced melanoma. **Methods:** TILVANCE-301 (NCT05727904) is a phase 3, multicenter, randomized, open-label, parallel group, treatment study that will randomize ~670 pts (1:1) to either Arm A: lifileucel plus pembro (study intervention includes tumor tissue resection, pembro, nonmyeloablative lymphodepletion [NMA-LD], lifileucel infusion, an abbreviated course of high-dose IL-2, and thereafter, continued pembro) or Arm B: pembro alone. Pts in Arm B who receive pembro and experience confirmed progressive disease verified by blinded independent review committee (BIRC) have the option to receive lifileucel as the immediate next line of treatment. Eligible adults have histologically confirmed advanced melanoma (Stage IIIC, IIID, or IV); ECOG PS of 0 or 1; estimated life expectancy $>$ 6 mo; $\geq$1 resectable lesion ~1.5 cm in diameter postresection to generate lifileucel and $\geq$1 measurable lesion (RECIST v1.1); and adequate hematologic parameters and organ function. Neoadjuvant or adjuvant treatment including ICI meeting protocol-specified criteria may be allowed. Exclusion criteria include prior therapy for metastatic disease; symptomatic untreated brain metastases; organ allograft or prior cell transfer therapy; uveal/ocular melanoma; chronic systemic steroid therapy; active systemic infections; cardiovascular, respiratory, or immune system illnesses; primary/acquired immunodeficiency; or other primary malignancy in the last 3 y. The dual primary efficacy endpoints are BIRC-assessed (RECIST v1.1) ORR and PFS. Key secondary efficacy endpoint is OS. Additional secondary efficacy endpoints include BIRC-assessed CR rate, DOR, and EFS; investigator-assessed ORR, PFS, CR rate, DOR, EFS, and PFS2; and safety as characterized by severity and seriousness of TEAEs, and relationship to study drug. The study will enroll globally. Clinical trial information: NCT05727904. Research Sponsor: This study is sponsored by Iovance Biotherapeutics.

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TPS9609 **Poster Session**

The DIET study: A randomized controlled trial of a high fiber diet in cancer patients (pts) receiving immune checkpoint blockade (ICB).

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Background: Gut microbiome modulation is a promising strategy to enhance response to ICB Fecal microbiota transplant studies have shown positive signals of improved outcomes in both ICB naïve and refractory melanoma; however, this strategy is challenging to scale. Diet is a key determinant of the gut microbiota and we have previously shown that a) habitual high dietary fiber intake is associated with improved response to ICB and b) fiber manipulation in mice impacts ant-tumor immunity. We recently demonstrated feasibility of a controlled high-fiber dietary intervention (HFDI) conducted in melanoma survivors with excellent compliance and tolerance. Building on this, we are now conducting a single center Phase II randomized trial of HFDI versus healthy control diet in cancer pts receiving ICB (NCT04645680). **Methods:** 57 pts starting standard of care (SOC) ICB will be enrolled in 4 cohorts: 3 melanoma cohorts in the adjuvant (n = 21), neoadjuvant (n = 12), and unresectable (n = 12) settings and 1 metastatic renal cell carcinoma (RCC) cohort (n = 12). Key inclusion criteria include BMI 18.5-40 kg/m2, and willingness to exclusively eat the diet. Key exclusion criteria include diabetes mellitus, inflammatory bowel disease, total colectomy or bariatric surgery, recent use of prebiotic/probiotic supplements, steroids (within 14 days), antibiotics (within 21 days), current smoker or heavy drinker, and dietary fiber $>$ 20g/day. Pts are randomized 2:1 to the HFDI (target fiber 50g/day) or control diet (fiber 15-20g/day) stratified by BMI and cohort. Both diets have same macronutrient composition but differ in fiber content. The primary objective is to establish the effects of a dietary intervention on the structure and function of the gut microbiome. Secondary endpoints include change in circulating and stool metabolites, systemic and tumor immunity, and safety and tolerability of dietary intervention. As a controlled feeding study, all meals are isocaloric and prepared by MD Anderson Bionutrition Research Core for up to 11 weeks. Meals follow American Cancer Society and American Institute for Cancer Research recommendations which include whole foods plant-forward diet, little to no processed meats or added sugars, and no alcohol consumption. Meals are shipped weekly within the contiguous United States and include breakfast, lunch, dinner, and snacks. The HFDI group start at 30g fiber/day, up titrated every 2 weeks up to 50g/day based on tolerance. Blood and stool samples are collected longitudinally. Tumor biopsies are required in the neoadjuvant cohort and optional in unresectable. A Fitbit is provided to monitor physical activity and a scale to measure daily weight. 24 of the planned 57 pts have been enrolled: n = 13 adjuvant, n = 5 neoadjuvant, n = 5 unresectable, n = 1 RCC. 14 treated with PD1 monotherapy, 9 with ipilimumab + nivolumab, and 1 with nivolumab + relatlimab. Clinical trial information: NCT04645680. Research Sponsor: Seerave Foundation; Elkins Foundation, Rising Tide Foundation, Mark Foundation.

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TPS9610 **Poster Session**

A phase 2 study to determine the pathological (path) response to neoadjuvant nivolumab (nivo) and relatlimab (rela) in high-risk stage II cutaneous melanoma: NeoReNi II.

Maria Gonzalez, Alexander Christopher Jonathan Van Akkooi, Andrew John Spillane, Sydney Ch'ng, Kerwin Frank Shannon, Jonathan Stretch, Michael Alexander Rtshiladze, Thomas Pennington, Robyn P.M. Saw, Alexander M. Menzies, Robert V Rawson, Linda Martin, Pascale Guitera, Mary Jane Gregorio, Kevin London, Rony Kapoor, Edward Hsiao, Serigne N. Lo, Richard A. Scolyer, Georgina V. Long; Melanoma Institute Australia, Sydney, Australia; Melanoma Institute Australia, Wollstonecraft, Australia; Melanoma Institute Australia, Royal Prince Alfred Hospital, Chris O'Brien Lifehouse, The University of Sydney, The Mater Hospital Sydney, Sydney, Australia; Melanoma Institute Australia, University of Sydney, Chris O'Brien Lifehouse, Sydney, Australia; Melanoma Institute Australia, Mater Hospital, Royal Prince Alfred Hospital, The University of Sydney, Sydney, Australia; Melanoma Institute Australia, Wollstonecraft, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Royal Prince Alfred Hospital, The Mater Hospital Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Melanoma Institute Australia, Royal Prince Alfred Hospital, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, Sydney Melanoma Diagnositic Centre at Royal Prince Alfred Hospital, Australia, Sydney, Australia; Sydney Children's Hospitals, Alfred Nuclear Imaging, University of Sydney, Sydney, Australia; Melanoma Institute Australia, I-Med radiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; Royal North Shore Hospital, I-Med Radiology, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Charles Perkins Centre, The University of Sydney, Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, Australia

Background: Patients diagnosed with stage II melanoma account for ~50% of those who develop metastatic disease and die (Poklepovic et al., 2020). Neoadjuvant therapy (NAT) is a powerful treatment platform to rapidly assess drug activity in resectable cancers using the International Neoadjuvant Melanoma Consortium (INMC) path response criteria (Tetzlaff et al., 2018), wherein a major path response (≤10% viable tumor) correlates with low risk of recurrence in resectable stage III melanoma (Menzies et al., 2021). Other benefits include early insight into response, feedback to pts regarding their individual response and prognosis, ability to tailor subsequent management, and collection of translational specimens to explore mechanisms of response and resistance (Amaria et al., 2019). NAT for stage II melanoma is an opportunity to improve survival rates beyond the gains achieved with adjuvant therapy, as illustrated by the phase II SWOG 1801 trial (Patel et al., 2022) for pts with stage III melanoma. The NeoReNi II trial will examine whether combination PD-1 blockade plus lymphocyte-activation 3 (LAG3) checkpoint inhibition will achieve a high rate of path response with manageable toxicity. **Methods:** Pts with histologically confirmed AJCC (8^{th} ed.) clinical stage IIA (T2b, T3A), IIB (T3b, T4a), or IIC (T4b) primary cutaneous melanoma from a partial biopsy, with residual macroscopic disease at study entry, are eligible (N = 20). Pts with IIA disease must have an estimated ≥20% risk of recurrence at 5 years, according to the Melanoma Institute Australia stage II risk calculator (melanomarisk.org.au). All pts undergo wide excision and sentinel lymph node resection (RES) at wk 6 following NAT with 2 doses of nivo (480 mg, IV) plus rela (160 mg, IV). Pts with no (> 50% viable tumor) or partial path response (> 10% - ≤50% viable tumor) receive a further 11 cycles (Q4W) of adjuvant nivo (480 mg) plus rela (160 mg), and radiological and clinical surveillance. Pts with complete (pCR; 0% viable tumor) or near-complete (≤10% viable tumor) path response will undergo radiological and clinical surveillance after RES. All pts will be followed for recurrence (6 monthly CT) and survival for 10 years. Lymphatic mapping, dermoscopy, in vivo confocal microscopy, CT, and FDG PET/CT will be performed at baseline (BL) and prior to RES to measure response to NAT. Tumour and fecal samples are collected at BL, RES, and recurrence. Blood samples are collected at BL, wk 4, RES, and recurrence. The primary endpoint is the rate of pCR at RES after 6 wks of NAT using INMC response criteria (Tetzlaff et al., 2018). Secondary endpoints include assessing the feasibility of NAT in a stage II pt population, RFS, OS, safety/tolerability, surgical outcomes, changes in confocal microscopy and dermoscopy, rate of sentinel node positivity and changes in lymphatic mapping, QOL, and biomarker analyses. Clinical trial information: NCT05418972. Research Sponsor: BMS; Melanoma Institute Australia.

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TPS9611 **Poster Session**

KEYVIBE-010: Adjuvant coformulated vibostolimab with pembrolizumab versus adjuvant pembrolizumab in patients with high-risk stage II-IV melanoma.

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Background: Pembrolizumab is an anti−PD-1 monoclonal antibody that has been shown to significantly improve recurrence-free survival and distant metastasis-free survival when used as adjuvant therapy in patients with high-risk resected melanoma (Long GV, et al. *Lancet Oncol*. 2022;23:1378-88; Eggermont AMM, et al. *Lancet Oncol*. 2021;22:643-54). Combining pembrolizumab with other therapies may further improve outcomes in this setting. Vibostolimab is an anti-TIGIT monoclonal antibody that showed antitumor activity and manageable safety when used in combination with pembrolizumab in patients with advanced solid tumors in the phase 1 KEYVIBE-001 study (Niu J, et al. *Ann Oncol*. 2022;33:169-80). The randomized, double-blind, phase 3 KEYVIBE-010 study (NCT05665595) is designed to evaluate the efficacy and safety of adjuvant coformulated vibostolimab and pembrolizumab (MK-7684A) versus pembrolizumab alone in patients with resected high-risk stage IIB-IV melanoma. **Methods:** Eligible patients are ≥12 years of age (weighing ≥40 kg if < 18 years), with surgically resected stage IIB or IIC (pathologic or clinical), III, or IV cutaneous melanoma per AJCC 8th edition guidelines, and an Eastern Cooperative Oncology Group performance status of 0 or 1 (Lansky play-performance scale ≥70 if < 16 years; Karnofsky performance status ≥70 if ≥16 to < 18 years). Patients must not have received any prior systemic therapy beyond complete resection and no more than 12 weeks can have elapsed between final surgical resection and randomization. Patients with ocular, mucosal, or conjunctival melanoma, and prior allogeneic tissue/solid organ transplant are excluded. Patients will be stratified by risk. Approximately 1560 patients will be randomly assigned 1:1 to receive intravenous coformulated vibostolimab 200 mg with pembrolizumab 200 mg or pembrolizumab 200 mg (2 mg/kg up to a maximum of 200 mg for adolescents) every 3 weeks. Treatment will continue for 17 cycles or until disease recurrence, unacceptable toxicity, or withdrawal. The primary end point is recurrence-free survival by investigator review. Secondary end points are distant metastasis-free survival by investigator review, overall survival, safety and tolerability, and quality of life. Hazard ratios and 95% confidence intervals will be estimated using a stratified Cox regression model with the Efron method of handling ties, with treatment as a covariate. Between-treatment differences will be evaluated using a stratified log-rank test. Enrollment is ongoing. Clinical trial information: NCT05665595. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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TPS9612 **Poster Session**

NADOM trial: Neoadjuvant/adjuvant trial of darovasertib in ocular melanoma (OM).

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Background: Darovasertib (Daro) is a novel inhibitor of PKC, that has pre-clinical activity in GNAQ/GNA11 tumours including ocular melanoma. A recently completed clinical trial of Daro monotherapy in metastatic OM with a response rate of 11%, and DCR of 78% with only mild manageable toxicity, suggesting utility in localized disease and in the adjuvant setting. **Methods:** NADOM is an investigator-initiated window-of-opportunity phase 2 clinical trial open in 3 centers across Australia. Eligible patients include patients planned for enucleation, ECOG 0-1 with adequate organ function. The primary objective is the feasibility and safety of neoadjuvant Daro in a pilot cohort of 12 patients. Secondary objectives include the effect of Daro on circulating biomarkers (including CTCs and ctDNA), imaging assessments (MRI, FDG-PET and ocular ultrasound), pharmacokinetic and pharmacodynamic correlates and radiographic PFS in the adjuvant setting. Treatment comprises a neo-adjuvant period of treatment of up to 6 months at ophthalmologist discretion with Daro (300mg bid) before definitive management. Patients who demonstrated radiological, biomarker or clinical response are then offered an adjuvant period of treatment for up to 6 months following integrated consensus at multi-disciplinary ocular oncology meetings. DSMB meetings are scheduled to ensure clinical and peri-operative safety regularly. Enrolment commenced in November 2022 and accrual is ongoing in the 6 month neo-adjuvant cohort. **Results:** To date, an initial safety cohort of 1 month of neo-adjuvant treatment has been cleared following DSMB review. **Conclusions:** Recruitment is ongoing and expected to complete in late 2023. Clinical trial information: NCT05187884. Research Sponsor: Ideaya Biosciences.

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TPS9613 **Poster Session**

PLUME: A single-arm phase II trial evaluating the combination of pembrolizumab and lenvatinib in metastatic uveal melanoma (mUM) patients (pts) previously treated or not with tebentafusp.

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Background: Up to 50% of pts with uveal melanoma (UM) develop metastases, mainly hepatic, with poor overall survival and limited treatment options as response rate to first-line immune checkpoint inhibitors (ICI) is low in mUM pts. Tebentafusp, a bispecific T-cell engager, was recently approved in this setting but only in HLA A*02-01+ mUM patients. Lenvatinib is a tyrosine kinase inhibitor targeting multiple growth factor receptors including vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFRs) and colony-stimulating factor receptor (CSF1-R), which are key pathways in UM. Lenvatinib showed an immune-modulating effect in preclinical models. The combination demonstrated synergic clinical anti-tumor activity in various tumor types including microsatellite-stable endometrial cancers, kidney cancers and ICI-resistant skin melanomas. We hypothesize that combining pembrolizumab with lenvatinib in mUM may lead to an improved immune response in mUM patients. **Methods:** Fifty-four, ICI-naïve, metastatic UM pts will be enrolled in this monocentric, single-arm phase II trial at Institut Curie, Paris, France. Because previous exposure to tebentafusp might increase the activity of subsequent ICI, the combination will be assessed in two independent cohorts: cohort 1 with HLA A*02-01^{neg}, tebentafusp-naive patients (22 assessable patients), and cohort 2 with HLA A*02-01^{pos} pts previously treated with tebentafusp (28 assessable patients). Up to 54 patients may be included according to an 8% drop-out rate. Each participant will receive pembrolizumab (200 mg Q3W, maximum of 35 cycles) plus lenvatinib (starting at 20mg QD) until reaching a discontinuation criterion. Liver MRI and chest-abdomen-pelvis CT will be performed every 9 weeks until progressive disease. Primary objective is to evaluate the progression-free survival (PFS) after nine cycles of treatment (27 weeks) as assessed by the investigator using the RECIST v1.1. Secondary objectives include PFS according to immune RECIST (iRECIST), overall survival, overall response rate, safety and tolerability, quality of life. Inclusion period started mid-July 2022 for two years. To date, twenty-four (21 in cohort 1, 3 in cohort 2) of planned 54 pts have been enrolled in six months. Biospecimens (longitudinal blood samples and tumor tissue at inclusion) will be collected during the study to allow biomarker research. Clinical trial information: NCT05282901. Research Sponsor: INCa PHRC-K 2020; Merck Sharp & Dohme LLC.

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TPS9614 **Poster Session**

CemiplimAb-rwlc survivorship and epidemiology (CASE): A prospective study of safety and efficacy of cemiplimab in patients with advanced basal cell carcinoma in a real-world setting.

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Background: Basal cell carcinoma (BCC) is the most common form of non-melanoma skin cancer in the United States. Surgical excision is the standard treatment, with $< 1\%$ of cases progressing to locally advanced or metastatic disease. Hedgehog pathway inhibitors (HHIs) are the first-line therapy for advanced BCC (aBCC); the US Food and Drug Administration and European Medicines Agency have approved the use of cemiplimab (a programmed cell death-1 inhibitor) in advanced BCC (aBCC) patients previously treated with (or are inappropriate for) HHI. Limited real-world data exist on the clinical characteristics, disease management and progression, and survivorship of patients with aBCC. The ongoing C.A.S.E. study aims to evaluate the efficacy, safety, disease evolution, survivorship, and patient reported outcomes (PRO) in patients treated with cemiplimab in the real-world setting. **Methods:** This trial in progress (NCT03836105) aims to describe the effectiveness and safety of cemiplimab 350 mg administered every 3 weeks for treatment of patients with aBCC in real-world clinical settings. Up to 100 adult patients with aBCC who are prescribed commercially available cemiplimab from ~65 study sites in the United States will be included. The duration of follow-up will be 24 months. Endpoints for this study relate to real-world efficacy, including overall survival; progression-free survival; objective response rate, (partial or complete response); and disease control rate, defined as the percentage who do not progress for ≥ 6 months; Time to response, duration of response, time to treatment failure, and disease-specific death will also be assessed. Real-world safety outcomes will also be captured, including immune-related adverse events, infusion-related reactions, and serious adverse events. Patient selection criteria and treatment patterns will be analyzed using descriptive statistics. This study also aims to describe the patient experience of real-world treatment with cemiplimab. PROs including global quality of life, functioning, and symptoms will be captured at baseline and follow-up visits via the EORTC QLQ-C30 and the Skin Care Index. Recruitment for this trial is ongoing. Clinical trial information: NCT03836105. Research Sponsor: Regeneron Pharmaceuticals, Inc.

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