Long-term follow up for adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma: Final results of the COMBI-AD study.

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Background: Dabrafenib plus trametinib, a standard-of care adjuvant treatment for patients with BRAF-mutated AJCC-stage III melanoma, has significantly improved the primary endpoint, relapse-free survival (RFS). Further to published interim assessments, we present updated and final results for RFS, distant-metastasis-free survival (DMFS) and overall survival (OS). **Methods:** In the COMBI-AD phase 3 study, patients received dabrafenib (150 mg BD) plus trametinib (2 mg OD; n=438) or matching placebos (n=432). Treatment continued for up to 12 months or until disease relapse, unacceptable toxicity, withdrawal of consent, or death. OS, RFS, and DMFS were summarized using Kaplan–Meier estimates. OS was compared between study arms using stratified log-rank test. Hazard ratio (HR) was calculated using Pike estimator. Safety data were summarized descriptively. **Results:** At final analysis, median duration of follow up was 100.0 months in the treatment arm and 82.5 months in the placebo arm. Median OS was not attained in the two arms (HR: 0.80; 95% CI: 0.62, 1.01; P=0.063). Consistent OS benefits were seen across most prespecified subgroups including patients with BRAFV600E mutation (n=397; HR: 0.75; 95% CI: 0.58, 0.96). Estimated RFS (HR: 0.52; 95% CI: 0.43, 0.63) and DMFS (HR: 0.56; 95% CI: 0.44, 0.71) favored the dabrafenib plus trametinib arm. In both arms, patients received salvage immunotherapies (29% each) and targeted therapy (21% vs. 37% for treatment and placebo arms, respectively). Safety profile was consistent with previous reports. **Conclusions:** COMBI-AD presents the longest follow-up data (over 10 years) in adjuvant treatment of stage III melanoma in the modern era. OS was improved with dabrafenib plus trametinib over placebo for adjuvant treatment of stage III melanoma with a 20% risk reduction for death. However, this difference was not statistically significant. Consistent with published results at 3 and 5 years, RFS and DMFS were more favorable in the treatment vs. placebo arm. Clinical trial information: NCT01682083. Research Sponsor: None.

Overall survival rate over long-term follow up.

		Year 1	Year 3	Year 5	Year 7	Year 8
Dabrafenib plus trametinib (N=438)	OS rate (%)	97	86	79	73	71
Dabrafenib plus trametinib (N=438)	No at risk	395	336	294	251	240
Placebo (N=432)	OS rate (%)	94	77	70	66	65
Placebo (N=432)	No at risk	377	282	248	216	201

OS, overall survival. Number at risk at end of time interval.

LBA9501 **Oral Abstract Session**

Phase 3 study (PIVOTAL) of neoadjuvant intralesional daromun vs. immediate surgery in fully resectable melanoma with regional skin and/or nodal metastases.

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9502 Oral Abstract Session

A randomised, controlled, multicentre trial of imiquimod versus radiotherapy for lentigo maligna.

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Background: Lentigo maligna (LM) is a form of melanoma in situ that occurs mainly on sun exposed skin. For patients with LM who are not suitable for surgery due to location, size, patient preference or co-morbidities, topical imiquimod or radiotherapy are alternative non-surgical treatments. There are no prospective randomized controlled trial data to form the basis of any recommendations for the management of LM. This multi-institutional, international randomized phase 3 trial evaluated the efficacy and safety of imiquimod verus radiotherapy for patients with LM. The primary hypothesis was that treatment of LM with topical imiquimod would result in fewer treatment failures than radiotherapy. **Methods:** Patients aged > 18 years old with LM not suitable for surgery were randomly assigned (1:1) to imiquimod or radiotherapy. The primary endpoint was treatment failure within 24 months. Secondary endpoints included development of invasive disease within the area, side effects and patient-reported quality of life (QOL) assessed with validated questionnaires (skin-specific Skindex-16 and generic EQ-5D-5L). **Results:** Between August 2015 and November 2021, 126 patients were randomised from 8 centres (imiquimod 60, radiotherapy 58 in final analysis). The median age was 72 years and 94.9% of lesions were on the head and neck area. Median follow-up was 27 months (range 3-62 months). Six (10.5%) patients in the imiquimod group and 12 (24.0%) patients in the radiotherapy group developed recurrence within 24 months (OR 2.68, 95% CI, 0·92-7.8, p = 0.063). Median time to recurrence was not reached in either group. Treatment failure was significantly different within the subgroup of patients who had reflectance confocal microscopy (RCM) follow up of the LM (imiquimod 4/46, 8.7% radiotherapy 13/52 25.0%; OR 3.50 95% CI 1.05-11.65, p = 0.033). Only one RCM feature was associated with failure at 24 months and significantly different between treatment groups : the presence of atypical round cells at the dermal-epidermal junction (6.9 % of imiquimod failure and 27% of radiotherapy failure: p = 0.035). There were no differences between trial groups in patient-reported skin symptoms (itching, burning/stinging, pain, irritation), skin-specific emotional and functional QOL impacts, or generic QOL at any time points. **Conclusions:** Both imiquimod and radiotherapy are valid, well-tolerated and efficient non-surgical options for LM. There is no significant difference in the acute or long term QoL for the two treatments. Clinical trial information: NCT02394132. Research Sponsor: Cancer Australia PdCCRS Grant; Royal Australia and New Zealand College of Radiologists.

LBA9503 **Oral Abstract Session**

Combination of encorafenib and binimetinib followed by ipilimumab and nivolumab versus ipilimumab and nivolumab in patients with advanced *BRAF*-V600E/K-mutated melanoma: The primary analysis of an EORTC randomized phase II study (EBIN).

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Efficacy and safety of triplet nivolumab, relatlimab, and ipilimumab (NIVO + RELA + IPI) in advanced melanoma: Results from RELATIVITY-048.

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Background: NIVO (anti–PD-1 antibody) is approved as monotherapy and in combination with either RELA (anti–LAG-3 antibody) or IPI (anti–CTLA-4 antibody) for the treatment of patients (pts) with advanced melanoma. RELATIVITY-048 (NCT03459222) is a phase 1/2, nonrandomized trial evaluating immuno-oncology (I-O) triplets, including NIVO + RELA + IPI, for pts with select solid tumors. This analysis from RELATIVITY-048 focused on NIVO + RELA + IPI use in the advanced melanoma cohort and is the first disclosure from the study. **Methods:** Pts with advanced melanoma were treated with first-line NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W until progression or unacceptable toxicity. Prior neoadjuvant/adjuvant therapy, including I-O agents, was permitted if completed > 6 mo before enrollment. Pts with controlled brain metastases were allowed to enroll. Primary endpoints were safety and confirmed objective response rate (ORR), disease control rate (DCR), and median duration of response (DOR) per investigator. The secondary endpoint was progression-free survival (PFS) per investigator (median and 6-mo/12-mo rates). Exploratory endpoints included overall survival (OS; median and 12-mo/24-mo rates). **Results:** In total, 46 pts were treated. Median follow-up was 44.1 mo (range, 0.4–53.5; database lock, Nov. 1, 2023). Median age was 61.0 y, 8.7% had cutaneous acral melanoma, 50.0% were *BRAF* positive, 73.9% were LAG-3 positive (≥ 1%), 26.1% were tumor cell PD-L1 positive (≥ 1%), and 6.5% had received prior adjuvant therapy. Median duration of treatment was 5.0 mo (range, 0.0–49.0). NIVO + RELA + IPI had a confirmed ORR of 58.7% and a 48-mo OS rate of 69.1% (**table**). Any-grade and grade 3/4 treatment-related adverse events (TRAEs) occurred in 44 pts (95.7%) and 18 pts (39.1%), respectively. Any-grade TRAEs led to treatment discontinuation in 19 pts (41.3%). Deaths due to TRAEs occurred in 2 pts (4.3%; rectal hemorrhage and dyspnea [n = 1], immune-mediated myositis [n = 1]). **Conclusions:** In RELATIVITY-048, NIVO + RELA + IPI demonstrated encouraging efficacy, with a confirmed ORR of 58.7% and a 48-mo OS rate of 69.1%. There were no new safety signals with NIVO + RELA + IPI, and the safety profile was generally consistent with I-O combinations. Given the small sample size, additional studies are needed to confirm the efficacy and safety of NIVO + RELA + IPI. Clinical trial information: NCT03459222. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA + IPI (n = 46)
Confirmed ORR, % (95% CI)	58.7 (43.2–73.0)
Confirmed DCR, % (95% CI)	76.1 (61.2–87.4)
Confirmed CR/PR/SD rates, %	17.4 / 41.3 / 17.4
Median DOR, mo (95% CI)	NR (NR–NR)
Median PFS, mo (95% CI)	NR (3.94–NR)
24-mo/48-mo PFS rates, % (95% CI)	57.2 (40.8–70.5) / 51.6 (35.3–65.6)
Median OS, mo (95% CI)	NR (NR–NR)
24-mo/48-mo OS rates, % (95% CI)	79.8 (64.8–89.0) / 69.1 (52.6–80.9)

CR, complete response; NR, not reached; PR, partial response; SD, stable disease.

9505 Oral Abstract Session

Efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, and pembrolizumab in patients with immune checkpoint inhibitor-naive unresectable or metastatic melanoma: Updated results from IOV-COM-202 cohort 1A.

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Background: Immune checkpoint inhibitors (ICI) are front-line standard-of-care treatment (tx) for advanced (unresectable or metastatic) melanoma. Despite recent advances in front-line tx, a majority of patients (pts) do not achieve long-term benefit. Lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, potentially induces durable responses in pts with advanced melanoma previously treated with ICI. This study evaluates lifileucel combined with anti-PD-1 therapy in front-line advanced melanoma. **Methods:** IOV-COM-202 (NCT03645928) Cohort 1A assesses the efficacy and safety of lifileucel and pembrolizumab (pembro) in pts with ICI-naive unresectable or metastatic melanoma. Pts may have received BRAF/MEK inhibitor tx if BRAF mutation-positive. Eligible pts must have ≥1 resectable lesion (≥1.5 cm diameter) for 22-day cryopreserved lifileucel manufacturing, and ≥1 measurable lesion for response assessment per RECIST v1.1. The tx regimen consists of pembro, nonmyeloablative lymphodepletion (cyclophosphamide and fludarabine), a single lifileucel infusion ($1 \times 10^9 - 150 \times 10^9$ cells), ≤6 doses of IL-2 (600,000 IU/kg IV), and continued pembro until disease progression, or unacceptable toxicity for ≤24 months. The endpoints are investigator-assessed objective response rate (ORR) and incidence of grade ≥3 treatment-emergent adverse events (TEAE). **Results:** As of 22-Dec-2023, 22 pts with a median (range) age of 48.5 (18–68) years received lifileucel and pembro. At baseline, the median (range) target lesion sum of diameters was 54.5 (14–355) mm; 7 (31.8%) pts had liver lesions. Metastatic staging at study entry was as follows: 4 (18.2%) had M1a, 2 (9.1%) had M1b, 10 (45.5%) had M1c, and 2 (9.1%) had M1d. Eight (36.4%) pts had V600 BRAF mutations; 3 (13.6%) pts had prior BRAF/MEK inhibitor tx. Confirmed ORR was 63.6% (14/22), including 22.7% (5/22) CR and 40.9% (9/22) PR; 6 pts (27.3%) had SD. Median time to initial response was 2.5 months. All response evaluable pts demonstrated regression of target lesions. At a median follow-up of 17.2 months, median duration of response was not reached. Responses deepened over time; 10/14 (71.4%) pts had ongoing response and 8/14 (36.4%) pts had response ≥12 months. TEAEs were consistent with the underlying disease and known safety profiles of pembro, nonmyeloablative lymphodepletion, and IL-2. Most common grade ≥3 TEAEs were thrombocytopenia (68.2%), neutropenia (50.0%), and anemia (45.5%). **Conclusions:** These results demonstrate encouraging efficacy and durability for the combination of lifileucel and pembro and support its further evaluation in pts with untreated advanced melanoma in the phase 3 study TILVANCE-301 (NCT05727904). Clinical trial information: NCT03645928. Research Sponsor: Iovance Biotherapeutics (San Carlos, CA, USA).

Triplet combination treatments with pembrolizumab (pembro) for anti–PD-(L)1–refractory advanced melanoma: Preliminary results of the phase 1/2 KEYMAKER-U02A study.

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Background: Anti–PD-(L)1–refractory melanoma is a major challenge, and immunotherapy combination treatment may be useful in this patient population. The phase 1/2 KEYMAKER-U02A (NCT04305041) is a multi-arm, open-label, adaptive umbrella study designed to evaluate pembro + investigational agents for the treatment of anti–PD-(L)1–refractory melanoma. We report results from arm 1 (pembro + quavonlimab [qmab] (anti-CTLA4) + vibostolimab [vibo] (anti-TIGIT)), arm 2 [pembro + qmab + lenvatinib [len] (TKI)), and arm 3 (pembro + ATRA [all-trans retinoic acid]) of KEYMAKER-U02A. **Methods:** In all arms, adults had stage III/IV melanoma, ≥1 measurable lesion per RECIST v1.1, an Eastern Cooperative Oncology Group performance status score of 0 or 1, and disease progression on anti–PD-(L)1 therapy alone or in combination. Pts were randomized equally to open arms. In arm 1, pts received pembro 200 mg IV Q3W + qmab 25 mg IV Q6W + vibo 200 mg IV Q3W. In arm 2, pts received pembro 400 mg IV Q6W + qmab 25 mg IV Q6W + len 20 mg PO QD. In arm 3, pts received pembro 400 mg IV Q6W + ATRA 150 mg/m^2/day PO for 3 days Q3W. Pts received treatment for up to 2 y or until intolerable toxicity, disease progression, or pt withdrawal. Primary end points were safety and ORR per RECIST v1.1 by blinded independent central review (BICR). DOR per RECIST v1.1 by BICR was the secondary end point. PFS per RECIST v1.1 by BICR and OS were exploratory end points. Enrollment was planned for a maximum of 20 pts in each arm and enrollment could continue to up to 40 pts if an ORR of > 20% (5/20) was observed. Enrollment would then continue up to 100 pts if an ORR of ≥35% (14/40) was observed. **Results:** At data cutoff (Oct 18, 2022), 40 pts had been assigned to arms 1 and 2 and 20 pts to arm 3. Median (range) follow-up was 18.4 (1.7-24.5) mo in arm 1, 18.5 mo (1.6-25.4) in arm 2, and 2.7 mo (0.8-3.5) in arm 3. Efficacy is reported in the table. Treatment-related adverse events (TRAEs) occurred in 35 pts (88%) in arm 1, 38 pts (95%) in arm 2, and 15 pts (75%) in arm 3. Grade 3-5 TRAEs occurred in 11 pts (28%) in arm 1, 23 pts (58%) in arm 2, and 3 pts (15%) in arm 3; 1 pt in arm 2 died from a grade 5 TRAE (immune-mediated nephritis). **Conclusions:** Although objective responses were observed in some pts with anti–PD-(L)1–refractory melanoma, protocol-prespecified criteria for enrollment expansion were not met in any arm. The safety profile was manageable. Additional arms will be reported for this pt population with a high unmet need. Clinical trial information: NCT04305041. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Arm 1 (Pembro + Qmab + Vibo) n = 40	Arm 2 (Pembro + Qmab + Len) n = 40	Arm 3 (Pembro + ATRA) n = 20
ORR, n (%)	7 (18); 1 CR	11 (28); 2 CRs	0 (0)
DOR, median (range), mo	9.8 (1.0+ to 19.4+)	10.4 (2.3+ to 17.3+)	-
PFS, median (95% CI), mo	2.1 (2.1-3.7)	6.2 (4.2-8.3)	2.1 (1.9-2.1)
OS, median (95% CI), mo	NR (12.1-NR)	17.9 (14.5-21.4)	NR (NR-NR)

+indicates ongoing response. CR, complete response; NR, not reached.

9507 Oral Abstract Session

Phase 1 safety and efficacy of IMC-F106C, a PRAME × CD3 ImmTAC bispecific, in post-checkpoint cutaneous melanoma (CM).

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Background: IMC-F106C is a novel ImmTAC bispecific protein (PRAME × CD3). Dose escalation results showed robust T cell activation, T cell infiltration into tumor, and clinical activity in various solid tumors (NCT04262466; Hamid 2022). We present updated CM data from mono-therapy (mono) and anti-PD1 combination (combo) cohorts. **Methods:** HLA-A*02:01+ unresectable/metastatic (m) CM patients (pts) previously treated with immune checkpoint inhibitors (ICI) were eligible. Primary objectives were safety and selection of recommended dose; additional objectives were efficacy and ctDNA response (Natera, Guardant). Stable disease (SD) with any tumor reduction confirmed with ≥ 1 subsequent scan was analyzed based on association with overall survival (OS) for tebentafusp. Molecular response was defined ≥ 0.5 log [68%] ctDNA reduction by week 9. PRAME was tested by immunohistochemistry (IHC; PRAME+ defined as H-score ≥1). Efficacy is presented by PRAME− and PRAME+ (documented + and unknown) groups. IMC-F106C dosed IV with 2 step-up doses and weekly target dose (20-320 mcg mono, 160 mcg combo). Pembrolizumab (pembro) dosed at IV 400 mg Q6W. Data cutoff: Dec 2023. Median follow-up of mono was 11 months. **Results:** 46 mCM pts (40 mono, 6 combo) received IMC-F106C ≥ 20 mcg. All mono pts received prior ICI (100% anti-PD1, 88% anti-CTLA4); 25% had prior BRAF/MEK inhibitors. 35/40 mono pts were grouped by IHC as positive (25 PRAME+, 10 unknown) vs. 5 PRAME−. Adverse events (AEs) were consistent with prior experience. Most common AE was Grade 1/2 CRS (50%); mostly in first 3 weeks. No drug related AEs led to treatment discontinuation or death. Safety for pembro combo to date was consistent with the individual agents. 31/40 mono pts had a RECIST evaluable tumor assessment. The clinical benefit rate (CBR) of PR + SD was 61% (19/31). 35% (11/31) had any tumor reduction that was confirmed on ≥ 1 subsequent scan, including 4 PR (ORR 13%) and 7 SD (26 of 31 pts were PRAME+; the CBR in these was 65% and included all 11 (42%) with confirmed tumor reduction. In 5 PRAME−, there was no tumor reduction. Both median progression free survival (PFS) and 6-month OS rates were higher in PRAME + vs −: 4.5 vs 2.1 months and 94% vs 40%, respectively. 12/40 mono pts received therapy for > 6 months and 14/40 mono pts remain on therapy. 41% of ctDNA-evaluable, PRAME+ mono pts had a molecular response (9/22); this was associated with longer PFS and OS. Correlative biomarkers will be shared. **Conclusions:** IMC-F106C was well tolerated with promising clinical activity in ICI-pretreated, mCM patients without clinical options. Clinical activity, measured by any confirmed tumor reduction and ctDNA molecular response, is enriched in PRAME+ patients at ~40% and associated with longer PFS and OS. IMC-F106C can be combined with anti-PD1. A Ph 3 trial of IMC-F106C with nivolumab in 1st line mCM has been initiated (PRISM-MEL301; NCT06112314). Clinical trial information: NCT04262466. Research Sponsor: Immunocore.

9508 Oral Abstract Session

Safety and efficacy of first-in-class CXCR1/2 inhibitor SX-682 in combination with pembrolizumab (pem) in patients (pts) with metastatic melanoma (mMEL) with disease progression on anti–PD-1 therapy.

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Background: Outcomes for pts with mMEL remain sobering despite access to available immunotherapies as the majority of pts are resistant or become refractory to checkpoint blockade with no approved treatments. CXCR1 and CXCR2 (CXCR1/2) signaling mediate myeloid immunosuppression and MEL growth, inversely correlating with anti-PD-1 response and pt survival. SX-682 is an oral allosteric inhibitor of CXCR1/2. As a single agent, SX-682 increases tumor CD8+ T cell infiltration and inhibits tumor growth in mouse MEL. **Methods:** This phase 1 dose-escalation with expansion trial (NCT03161431) evaluated pem and escalating doses of SX-682 (25 - 400 mg orally BID) in pts with mMEL in a 21-day cycle. Pts must have had progressive disease (PD) on prior anti-PD-1. Mucosal MEL and asymptomatic brain metastases were allowed. Escalation cohorts had a 21-day SX-682 monotherapy (MONO) run-in. Response assessment by RECIST 1.1 was every 2 cycles during combination (COMBO) treatment. Primary endpoint was safety: adverse events (AEs), dose-limiting toxicity (DLT) and maximally-tolerated dose (MTD). Secondary endpoints included objective response rate (ORR; complete [CR] + partial [PR] response), disease control rate (DCR; CR + PR + stable disease [SD]) and overall survival (OS). **Results:** As of October 2023, 51 pts were enrolled and treated; median age of 65 (range 24-91), 55% male, 61% elevated LDH, 39% BRAF mutated. All pts received prior anti-PD-1, 37 (73%) received combined anti-PD-1 and anti-CTLA-4, and 23 (45%) had $\geq$ 3 prior therapies. Steady-state blood SX-682 was dose-proportional. No MONO DLT or MTD was identified. The 200 mg dose cohort was expanded in COMBO based on safety and pharmacodynamics: mg BID dose (n) = 25 (3), 50 (3), 100 (6), 150 (8), 200 (31). Any grade and grade 3/4 treatment-related AEs (TRAEs) occurred in 75% and 43%, respectively, and discontinuation (DC) due to TRAEs in 20% (when uncomplicated neutropenia, a permitted effect from CXCR2 inhibition on bone-marrow trafficking, was excluded there were 25% grade 3/4 TRAEs and 12% DC [rash, transaminitis]). There was no infectious signal. At the 200 mg dose, the ORR was 21% in 19 evaluable pts (4 PR + 0 CR) and the DCR was 63% (8 SD + 4 PR). DCR significantly depended on SX-682 dose (P vs. $\leq$100 mg): 0% (0/9) at $\leq$100 mg, 50% (3/6) at 150 mg (P = 0.0440) and 63% (12/19) at 200 mg (P = 0.0028). All 15 pts with disease control had progressed on anti-PD-1 and anti-CTLA-4. Median OS was longer in pts in the 200 mg cohort (14.7 months; 95% CI, 10.5 – NR [not reached], n = 31) than in pts treated with $\leq$100 mg SX-682 (7.4 months; 95% CI, 5.0 – NR; n = 10). **Conclusions:** SX-682 combined with pem had a tolerable safety profile and activity reflected by objective responses and clinically meaningful disease control in heavily pretreated mMEL pts with progression on anti-PD-1 and anti–CTLA-4. Clinical trial information: NCT03161431. Research Sponsor: Syntrix Bio; NIH CA217591.

9509 Rapid Oral Abstract Session

Phase II multi-center study of adjuvant nivolumab in combination with ipilimumab in patients with high-risk uveal melanoma (HCRN MEL17-309).

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Background: High-risk uveal melanomas (UM) recur distantly in over 50% by 3 years (median distant metastatic-free survival (DMFS) 32 months). No effective treatment currently exists to reduce the risk of metastatic disease and patients (pts) with metastasis have a very poor prognosis with few therapeutic options. The combination of Nivolumab/Ipilimumab (Nivo/Ipi) has shown limited efficacy in pts with metastatic UM. However, preclinical data suggest differential biology between local vs metastatic UM. We performed a prospective multi-center phase II study of adjuvant Nivo/Ipi in pts high-risk UM patients to compare DMFS to a cohort of UM with the same tumor characteristics. **Methods:** This investigator-initiated study enrolled pts with high-risk UM, defined as a predicted 3-year distant relapse-free survival (DMFS) of approximately 50% (based on gene expression profiling (GEP) (DecisionDx-UM) class 2 with tumor largest basal diameter (LBD) of 12mm or higher). Pts received Nivo 240mg iv every 2 weeks and Ipi 1mg/kg every 6 weeks for up to 48 weeks. The target sample size was 50 evaluable pts. The primary endpoint was 3-year DMFS. Secondary endpoints were median DMFS, overall survival (OS), and toxicity (AE). In addition, a propensity score method (double robust estimate in R adjusted curves) is used to estimate the average DMFS and compare the nonrandomized treatment (tx) and the control patients. 119 pts from the Cooperative Ocular Oncology Group (COOG) database were defined as high risk, matched for tumor characteristics (GEP class 2, LBD≧12mm) and were used as a control cohort. **Results:** Fifty-two pts were enrolled and 50 were treated from 12/18/2018-9/29/2021. As of 11/6/2023, with a median follow-up of 36 months, the 3-year DMFS rate vs COOG control, was 69.1% vs 45.1% (two-sided p = 0.012) without any adjustment; and 70.4% vs 43.4% (two-sided p = 0.018) with the propensity score method. The median DMFS was not reached (NR) in the tx cohort vs 33.8 months. There was a reduction in the risk of distant recurrence with Nivo/Ipi vs control cohort (RR 0.52, 95%CI, 0.309-0.888). Median OS has not been reached with only 7 deaths from UM in the tx cohort so far. Grade ≥3 any-cause AE occurred in 27 pts (54%). Grade ≥3 treatment-related (TR) AE occurred in 48%. 22 pts (44%) discontinued the treatment due to toxicity. One pt died due to immune-related myocarditis. **Conclusions:** This phase II study of adjuvant Nivo/Ipi resulted in clinically meaningful and statistically significant improvement in 3-year DMFS of 70.4% vs 43.4% in control for pts with high-risk UM from the COOG database matched for tumor characteristics. Further investigation of this regimen as adjuvant therapy of high-risk UM is warranted. Clinical trial information: NCT03528408. Research Sponsor: Bristol Myers Squibb.

9510 Rapid Oral Abstract Session

A phase 2 safety and efficacy study of neoadjuvant/adjuvant darovasertib for localized ocular melanoma.

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Background: Darovasertib is a protein kinase C (PKC) inhibitor with meaningful activity in metastatic uveal melanoma (UM) due to its effect on PKC delta downstream of canonical GNAQ/GNA11 mutations. To date, its clinical activity in patients with localized primary disease has not been assessed in either neoadjuvant or adjuvant settings. **Methods:** Patients planned for enucleation with localized UM were treated in an initial safety cohort with darovasertib 300mg BID for 1 month (n=3 patients), and then following DSMB agreement in an expansion cohort for up to 6 months (n=12 patients) as neoadjuvant treatment prior to definitive management (enucleation, plaque brachytherapy or EBRT) across 3 Australian centers. All patients were eligible to receive up to 6 months of adjuvant treatment with darovasertib at investigator discretion after definitive management of their primary tumour. Tumour volume was calculated by the rotational ellipsoid method. **Results:** 15 patients (male n=7, female n=8; median age 62 years (range, 33-76 years)) were enrolled. At baseline, AJCC tumor stages were T3a (n=5), T3b (n=4), T4a (n=4), T4b (n=2), and the median tumor size (maximum thickness/diameter/volume) was 9.7mm/ 15.6 mm/ 2463 mm^3. At datalock; 11/15 patients had completed primary treatment, 4/15 remained on neoadjuvant treatment, 6 patients received adjuvant darovasertib after primary treatment of their UM with 3 patients completing the planned 6-months . Median tumor shrinkage (maximum height/base/volume change) was 11.2%/ 7.6%/ 22.7% after 1 month of treatment and 31.7%/ 11.9% /45.3% after 6 months. At datalock, 6/9 (66%) currently completed neoadjuvant patients were converted to plaque brachytherapy (n=5) or EBRT (n=1) with 3 ongoing. One patient with high-risk cytogenetic features had relapsed with metastatic disease despite receiving 6-months of neoadjuvant darovasertib and another 6-months of adjuvant treatment. Treatment emergent adverse events included postural hypotension (Gr1/2 – 13/13%), syncope (Gr3 – 13%), rash (Gr1/2 – 33/5%), pruritis (Grr1 – 13%), dizziness (Gr1 – 27%), fatigue (Gr1/2 – 30/5%), nausea (Gr1/2 – 73/6%), vomiting (Gr1 – 40%), and diarrhea (Gr1 – 60%). Updated results, histopathological and genomic outcomes will be presented. **Conclusions:** NADOM provides the first evidence that a globe-salvage neoadjuvant treatment strategy in UM is feasible, safe, and efficacious. The results suggest that PKC inhibition with darovasertib can induce clinically meaningful tumor shrinkage in patients with primary UM patients who otherwise require enucleation. Larger trials are in now progress (NCT05907954) to further quantify visual and oncological outcomes. Clinical trial information: 05187884. Research Sponsor: Ideaya.

9511 Rapid Oral Abstract Session

Safety, efficacy, and biomarker results from an open-label, multicenter, phase 1 study of RP2 alone or combined with nivolumab in a cohort of patients with uveal melanoma.

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Background: Uveal melanoma is the most common primary intraocular tumor in adults and has a high risk of liver metastasis. Effective treatments for metastatic uveal melanoma (MUM) are limited, as MUM responds poorly to immune checkpoint inhibition. RP2 is an enhanced-potency oncolytic HSV-1–expressing human GM-CSF, a fusogenic glycoprotein (GALV-GP-R−), and an anti–CTLA-4 antibody-like molecule. We present safety, efficacy, and biomarker data for RP2 monotherapy and RP2 +nivolumab (nivo; anti–PD-1) in patients (pts) with MUM (NCT04336241). **Methods:** Pts ≥18 years old with advanced or metastatic non-neurologic solid tumors (including MUM) who progressed on, or could not tolerate, standard therapy were included in the clinical trial; pts had ≥1 measurable and injectable tumor (≥1 cm). After determination of the recommended phase 2 dose of intratumoral RP2 (1×10^6 PFU/mL once, then ≤7 doses at 1×10^7 PFU/mL; ≤10 mL total/treatment day), pts received RP2 Q2W as monotherapy or in addition to nivo (240 mg Q2W/480 mg Q4W). Responses were assessed per modified RECIST v1.1.Tumor biopsies and peripheral blood mononuclear cells were collected pre-treatment and at day 43 and were analyzed by immunohistochemistry (IHC) and/or sequencing of the CDR3β region of the T-cell receptor (TCR) by immunoSEQ. **Results:** A total of 17 pts with MUM were enrolled (RP2 monotherapy, n = 3; RP2 + nivo, n = 14). Most pts had received both anti–PD-1 and anti–CTLA-4 therapy (12/17 [70.6%]), and 3/17 (17.6%) had received ≥3 prior lines of therapy. The ORR was 29.4% (5/17; all PRs; RP2 monotherapy, 1/3; RP2 + nivo, 4/14). The DCR (CR + PR + SD) was 58.8% (10/17). The median (range) duration of response at the data cutoff was 11.5 (2.8–21.2) months, with some responses and disease stabilizations ongoing. The most common overall grade 1–2 treatment-related AEs (TRAEs; ≥20% overall) were pyrexia, chills, fatigue, hypotension, and pruritus. The only grade 3 TRAE in > 1 pt was hypotension (2 pts receiving RP2 + nivo); no grade 4/5 TRAEs occurred. Evaluable baseline and post-treatment biopsies were used for IHC (n = 8) and TCR sequencing analyses. Paired biopsies from pts with clinical benefit (n = 5; 2 PR, 3 SD) showed an increase in tumor PD-L1 expression by IHC analysis, and 4 of these pts (2 PR, 2 SD) exhibited an increase in CD8+ T-cell infiltration into tumors. TCR sequencing following treatment with RP2 + nivo revealed expansion of pre-existing TCRs and generation of new T-cell clones. **Conclusions:** RP2 alone or combined with nivo demonstrated a favorable safety profile and meaningful antitumor activity in pts with previously treated MUM. Biomarker data indicated immune cell infiltration and increased PD-L1 expression in tumors and changes in the peripheral T-cell repertoire following RP2 ± nivo therapy. Based on these results, a randomized, controlled clinical development plan is being planned. Clinical trial information: NCT04336241. Research Sponsor: Replimune, Inc.

LBA9512 **Rapid Oral Abstract Session**

Individualized neoantigen therapy mRNA-4157 (V940) plus pembrolizumab in resected melanoma: 3-year update from the mRNA-4157-P201 (KEYNOTE-942) trial.

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LBA9513 **Rapid Oral Abstract Session**

Combination or sequence of vemurafenib, cobimetinib, and atezolizumab in high-risk, resectable melanoma (NEO-TIM): Primary results.

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9514 Rapid Oral Abstract Session

A phase 2 study of de-escalation in resectable, locally advanced cutaneous squamous cell carcinoma (cSCC) with the use of neoadjuvant pembrolizumab: De-Squamate.

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Background: Neoadjuvant anti-Programmed Death therapy has shown a 64% complete or major pathological response rate in patients (pts) with resected stage II-IV(M0) cSCC. The De-Squamate study (NCT05025813) evaluated the feasibility of a risk adapted surgical de-escalation approach guided by clinical, radiological and pathological response in resectable cSCC pts of all sites receiving neoadjuvant pembrolizumab. **Methods:** This multi-centre, open-labelled, non-randomised, single-arm phase 2 study evaluated the response of neoadjuvant Pembrolizumab for 4 cycles administered IV 200mg Q3W in immunocompetent pts with Stage II-IV (M0) resectable cSCC. Pts underwent CT/MRI and 18F-FDG-PET imaging at baseline and following completion of neoadjuvant pembrolizumab. In those with a complete metabolic response, mapping biopsies of target site(s) were performed and if negative for residual SCC (clinical complete response [CCR]), surgery and post operative radiation therapy (PORT) were omitted. Patients with clinical or radiological residual disease/ positive mapping biopsy underwent surgical resection. PORT was de-escalated if there was a pathological complete response (PCR - no residual tumour cells) or major pathological response (MPR - less than or equal to 10% viable tumour cells). Pts proceeded to 13 cycles of maintenance Pembrolizumab. The primary endpoint was the combined rate of PCR, MPR and CCR following neoadjuvant Pembrolizumab and secondary endpoint includes treatment de-escalation and safety. **Results:** All 27 patients were enrolled and received a minimum of 2 cycles of neoadjuvant Pembrolizumab. The primary endpoint was observed in 17 patients (63%, 95% CI: 42-80), comprised of PCR (15%), MPR (0%) and CCR (48%). De-escalation of both surgery and PORT was achieved in 48% and a further 15% avoided PORT alone. With a minimum follow up of 6 months, no pts with PCR/MPR/CCR recurred. Investigator assessed treatment-related adverse events $\geq$ grade 3 was seen in 2 patients (7%). **Conclusions:** Pembrolizumab led to a high rate of PCR and CCR in resectable cSCC. The de-squamate study design effectively selected pts for surgical and PORT de-escalation and demonstrated a sustained response in this cohort. Clinical trial information: NCT05025813. Research Sponsor: MSD.

9515 Rapid Oral Abstract Session

OBX-115, an interleukin 2 (IL2)-sparing engineered tumor-infiltrating lymphocyte (TIL) cell therapy, in patients (pts) with immune checkpoint inhibitor (ICI)-resistant unresectable or metastatic melanoma.

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Background: Investigational unengineered TIL cell therapy has shown promising activity in ICI-resistant metastatic melanoma but requires systemic high-dose IL2, which has well-described high-grade toxicity frequently requiring specialized management and limiting pt eligibility. OBX-115 autologous engineered TIL cell therapy does not require co-administration of IL2 due to its regulatable expression of membrane-bound IL15 (mbIL15) using the FDA-approved small-molecule drug acetazolamide (ACZ) to provide cytokine support for TIL expansion and persistence. **Methods:** This Phase 1 study (NCT05470283) assesses the OBX-115 regimen in pts with ICI-resistant unresectable/metastatic melanoma. OBX-115 is manufactured from the pt's tumor tissue (surgical excision or core needle biopsy [CNB]). After lymphodepletion (cyclophosphamide, fludarabine), pts receive OBX-115 followed by ACZ once daily for up to 7 days; ACZ redosing (up to 7 days) is permitted at Wk 6 for non-responders. No systemic IL2 is administered. Peripheral blood and tumor tissue is collected for longitudinal immune profiling. **Results:** As of 02 Jan 2024, 9 pts (median age, 50 y) with ICI-resistant metastatic melanoma were infused with OBX-115 (median study follow up, 17 wks; range, 2–58 wks). Median lines of prior therapy was 3 (range, 1–6). OBX-115 was successfully manufactured for all pts, including from CNB tumor tissue (n = 5). The infusion product had a high proportion of CD8+ cells (≥96%) and stem-like cells (CD8+CD39-CD69-; median 76%) with very low PD-1 expression in the CD8+ population ($<$ 1%). Post-infusion safety included no DLTs, 3 Gr 3 nonhematologic TEAEs in 2 pts (abdominal pain, ALT elevation, syncope), and no Gr 4 nonhematologic TEAEs. ACZ was redosed and well-tolerated in 4 of 5 eligible pts. Among patients with minimum 12-wk follow-up (n = 6), ORR per RECIST v1.1 was 50% (2 CR, 1 PR, 3 SD); all responses occurred between Wk 6–18 and were ongoing, with longest response sustained $>$ 12 mo. One pt developed new metastatic disease (liver) and progressed at Wk 24, despite continued target lesion reduction; no pt developed brain metastasis. Post-infusion ctDNA was not detectable in any of the responders at Day 14 or 42. Though OBX-115 had minimal NK cells ($<$ 1%), post-infusion peripheral blood and tumor biopsies showed NK cell expansion, consistent with trans-presentation of mbIL15 to circulating NK cells. Updated efficacy data on all infused pts will be presented. **Conclusions:** OBX-115regulatableengineeredTIL cell therapy was well-tolerated and produced consistently deepening and durable responses, indicating that OBX-115 may mediate CRs and durable clinical benefit in ICI-resistant metastatic melanoma without high-dose IL2. OBX-115 investigation continues in this and an ongoing Phase 1/2 multicenter study (NCT06060613). Clinical trial information: NCT05470283. Research Sponsor: Obsidian Therapeutics, Inc.

LBA9516 **Rapid Oral Abstract Session**

Phase III randomized trial evaluating tilsotolimod in combination with Ipilimumab versus Ipilimumab alone in patients with advanced refractory melanoma (ILLUMINATE 301).

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9517 Rapid Oral Abstract Session

Efficacy and safety of RP1 combined with nivolumab in patients with anti–PD-1–failed melanoma from the IGNYTE clinical trial.

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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 pts with anti–PD-1–failed melanoma, including the initial cohort and updated data from a registration-directed (R-D) cohort, from the phase 1/2 IGNYTE study (NCT03767348). **Methods:** Pts had locally advanced or metastatic cutaneous melanoma with ≥1 measurable and injectable tumor (≥1 cm) and confirmed progressive disease (PD) while on therapy and received anti–PD-1 ± anti–CTLA-4 therapy for ≥8 consecutive weeks, with anti–PD-1 being the last treatment received. Pts on prior adjuvant anti–PD-1 therapy had confirmed PD while on adjuvant therapy. RP1 was initially given intratumorally at 1×10^6 plaque-forming units (PFU)/mL and then every 2 weeks (Q2W) at 1×10^7 PFU/mL for up to 8 total cycles (≤10 mL/cycle) combined with nivolumab (nivo; cycles 2–8, 240 mg IV); pts then received nivo alone (240 mg Q2W or 480 mg Q4W IV) for up to 2 years, with the option to receive additional courses of RP1 if specified criteria were met. **Results:** Overall, 156 pts were enrolled (initial melanoma cohort, n = 16; R-D cohort, n = 140); 46.2% of pts had been treated with prior anti–PD-1 combined with anti–CTLA-4, and 51.3% of patients had stage IVM1b-d disease. The overall objective response rate (ORR) was 31.4%, and 12.2% of pts achieved complete response (CR; **Table**). Responses were observed irrespective of prior anti–PD-1 therapy setting and disease stage (**Table**). Responses were seen in uninjected lesions and in bulky and visceral disease. The ORR for pts with primary anti–PD-1 resistance was 34.1%. In pts who failed prior ipilimumab + nivo, the ORR was 26.4% (**Table**). The median duration of response (time from baseline to end of response for responders) was > 24 months, with 100% of responses lasting > 6 months from baseline; 78% of responses were ongoing. Treatment-related adverse events (TRAEs) associated with RP1 + nivo were predominantly grade 1–2; there was 1 grade 5 TRAE (immune-mediated myocarditis attributed to nivo). **Conclusions:** The updated 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. Clinical trial information: NCT03767348. Research Sponsor: Replimune, Inc.

IGNYTE response data.[a]

	Pts N	CR n (%)	ORR n (%)
All patients[b]	156	19 (12.2)	49 (31.4)
Prior anti–PD-1			
Single agent anti–PD-1	84	14 (16.7)	30 (35.7)
Combination anti–PD-1 + anti–CTLA-4	72	5 (6.9)	19 (26.4)
Stage			
IIIb/IIIc/IVa	76	15 (19.7)	29 (38.2)
IVb/IVc/IVd	80	4 (5.0)	20 (25.0)

[a]Investigator-assessed responses.
[b]There are 5 pts still on study with the opportunity for response as of data cutoff (Nov 6, 2023).

A phase 2 clinical trial of regorafenib in patients with advanced pretreated melanoma (RegoMel).

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Background: A majority of advanced melanoma patients (pts) will eventually progress despite treatment with PD-(L)1/CTLA-4/LAG-3 immune checkpoint- and BRAF-/MEK-inhibitors (BRAF-/MEKi; restricted to *BRAF*^{V600}-mutant pts). Retrospective case observations indicate activity of regorafenib (REGO) in this setting (1). **Methods:** This single center, prospective, two-stage, phase 2 clinical trial, investigates REGO 80 mg QD (continuous dosing) in pts with advanced melanoma refractory to standard of care treatment. Objective response rate (ORR, by RECIST v1.1) served as the primary endpoint. The sample size (n=16) was determined according to a Simon's two-stage minimax statistical design; the trial is considered positive if 3 or more responses are observed. Response assessments are performed every 6 weeks (q6w) during the first 24w, and q12w thereafter. Secondary endpoints are safety, progression free survival (PFS) and overall survival (OS). REGO treatment beyond first progression was permitted if considered to be of potential clinical benefit. Database lock was on Jan 9th, 2024. **Results:** From Oct 2022 to Sep 2023, 16 pts were enrolled (9 male, med age 61y; AJCC stage IIIC: 1; IV-M1a: 1; -M1c: 12, -M1d: 2, ECOG PS 0-1: 100%). Oncogenic driver mutations were identified in *BRAF*^{V600}: 7-, *KIT*: 3-, *NF1*: 3-, *NRAS*^{Q61K}: 2-, *RAF* fusion: 1 pt. The ORR was 31% (: 5 partial responses (PR) - 4 confirmed in 3 *KIT*-,and1 *BRAF*^{V600}-mutpt; and1 unconfirmed in a *BRAF*^{V600}-mut pt). One *KIT*-mut pt had previously progressed on imatinib. The median duration of response (DoR) was 29.7w (range 12-44). The disease control rate (DCR) was 56%. The median time on REGO monotherapy was 12.3w [95% CI 2.3-22.3], treatment is ongoing in 3 pts. At first progression, 6 *BRAF*^{V600}-mut pts continued REGO in association with BRAF-/MEKi, in 5 response evaluable pts there is an ORR of 40% (2 PR with DoR of 24w and 30w) and DCR of 80%. At database lock, 11 pts were alive with a median follow up of 48.4w (range 24-63), 13 pts have progressed on REGO monotherapy (median PFS 11.9w [95% CI 3.5-20.3]; median OS was not reached). There were no grade $\geq$ 4 treatment related adverse events (TRAE); 56% of pts had at least one grade 3 TRAE, including hypertension (n=3) and maculo-papular rash (n=2). There was one toxicity-related REGO discontinuation. **Conclusions:** This phase 2 clinical trial on REGO monotherapy in advanced pretreated melanoma patients met its primary endpoint and demonstrated significant anti-tumor activity in *KIT*-mutant melanoma patients. In *BRAF*^{V600}-mutant melanoma, continuation of REGO in combination with BRAF-/MEK-inhibitors demonstrated promising activity in patients who previously progressed on BRAF-/MEK-inhibitors for which further prospective investigation is ongoing. 1. Dirven I. et al. ESMO Meeting 2023. Clinical trial information: NCT05370807. Research Sponsor: Universitair Ziekenhuis Brussel; Universitair Ziekenhuis Brussel.

LBA9519 **Poster Session**

Ipilimumab and nivolumab plus UV1, an anticancer vaccination against telomerase, in advanced melanoma.

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Outcomes following long-term response to immune checkpoint inhibitors in patients with advanced melanoma.

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Background: Immune checkpoint inhibitors (ICI) targeting PD-1 and CTLA-4 can achieve durable responses. Historically, therapies in advanced malignancies were considered palliative, however long-term results from ICI melanoma studies suggest cure may be possible for some patients (pts). Despite clinical trial data, little is known about the risk, character, and clinical outcome of late recurrences after ICI. **Methods:** ICI treated pts with advanced melanoma who had a long-term disease control, defined as not requiring a subsequent line of systemic therapy within 3 years, were retrospectively identified at 11 centres. Those who had progressive disease managed with local therapies were included if no new systemic therapy was commenced within the 3 years. Demographics, disease characteristics, treatment, toxicity, recurrence patterns, management and outcomes were collected. **Results:** 567 pts were identified, with a median follow up of 7 years since start of therapy. At ICI commencement, 41% and 17% had M1c or M1d disease respectively, 26% had an elevated LDH, 33% were BRAF mutant and 24% had received prior therapy. The ICIs received were anti-PD-1 +/- an investigational agent (59.3%), anti-PD-1 plus anti-CTLA-4 (35.8%), or an anti-CTLA-4 (5%). The median duration of therapy was 18 months, with 31% of pts stopping due to toxicity. 63 pts (11.1%) had oligo-progression within 3 years from ICI start. 53 pts (9.3%) had progression after 3 years, with median time to progression of 16.3 months. Subsequent late progression was more common in those who had oligo-progression within 3 years of treatment compared to those who had not (14/63, 22% vs 39/504, 7.7%, $P<0.001$). The risk of late progression was lower in those who achieved a complete response (CR) compared to those without a CR (23/369, 6.2% vs 30/198, 15.2%, $P<0.001$). The landmark 5 year PFS was 95% compared to 89% in those with or without a CR respectively. Duration of therapy, treatment cessation due to toxicity, or corticosteroid use were not associated with the risk of late progression. Most late progression occurred within year 3 to 5 (38/53, 72%). 15 pts who progressed after 3 years were managed with local therapy alone. In progressors retreated with PD-1 alone as the next subsequent therapy, 14 of 26 (54%) responded (7 CR, 7 PR). In the total cohort, there were 31 (5.5%) deaths, 7 (1.2%) from melanoma. Of the pts with a CR, 14 (3.7%) died, only 1 (0.3%) from melanoma. Of the 53 pts who progressed after 3 years, 10 (19%) died, 7 (13%) from melanoma. **Conclusions:** In this population of pts with advanced melanoma with long term disease control from ICI, the risk of subsequent disease progression and death was low (1.2%). Predictors for late progression after 3 years were a non-CR best response and prior progression within 3 years. This and other data suggest a significant proportion of long-term ICI responders are likely cured, and may inform frequency and duration of follow up. Research Sponsor: None.

9521 Poster Session

When to stop immunotherapy for advanced melanoma: Emulation of target trials.

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Background: Immune checkpoint inhibitors (ICI) have demonstrated their effectiveness with a 7.5-year overall survival (OS) close to 50% for advanced stages. The design of clinical trials allowed treatment until progression or toxicity, or for a maximum duration of two years. Prolonged follow-up of responders after cessation shows sustained response and a low risk of relapse in the months following cessation. As of yet, the optimal duration of anti-PD-1 therapy for metastatic melanoma remains unestablished. The objective of this work was to evaluate the optimal duration of ICI. **Methods:** We conducted emulated trials using the cloning, weighting and censoring approach. Each emulated trial aimed at comparing the causal effect of stopping versus continuing ICI at a specific timepoint, in patients still under treatment and with disease control at that time. **Results:** The study comprised 1017 participants to the MELBASE cohort. Results of the 6-month discontinuation emulated trial showed a significantly lower OS if treatment was discontinued, compared to continuing treatment for at least three months. The 48-month survival difference was 37.8% (95% confidence interval [CI] 19.8 to 60.5), and the corresponding restricted mean survival time difference 8.3 months (95% CI: 4.1 to 12.7). The 12-month and 18-month discontinuation emulated trials both showed no evidence of benefit of either discontinuing or continuing ICI at any of those timepoints. The 24-month discontinuation emulated trial results were more in favor of stopping compared to continuing treatment at that decision point, with an absolute 48-month survival 10.5% higher (95% CI 4.4 to 18.1). **Conclusions:** These results suggest that a one-year course of immunotherapy is both necessary and sufficient for patients with advanced melanoma. Prolonged treatment beyond 2 years does not appear to be beneficial in terms of survival and could even be detrimental. Research Sponsor: None.

Overall survival: analysis up to 36 months after the decision point. A positive survival difference or RMST differences indicate an average longer survival with ICI continuation at the decision timepoint.

Decision Timepoint	Time Horizon From Treatment Initiation (mo.)	Survival Difference (95% CI)	RMST Difference (95% CI)
6 months	48	37.8% (19.8 to 60.5)	+8.3 (4.1 to 12.7)
12 months	48	−3.7% (−14.1 to 8.3)	+0.7 (−1.8 to 4.5)
18 months	48	−4.2% (−14.9 to 5.4)	+0.4 (−1.5 to 2.5)
24 months	48	−10.5% (−18.1 to −4.4)	−1.0 (−1.8 to −0.3)

RMST: Restricted mean survival time.

Continuous intrathecal infusion of nivolumab in advanced melanoma with leptomeningeal disease.

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Background: The prognosis of melanoma patients with leptomeningeal disease (LMD) remains poor (median OS of 3.5 months). Intrathecal (IT) drug administration could bypass the blood-cerebrospinal fluid (CSF) barrier and has been explored in many cancers using chemotherapies or monoclonal antibodies. According to a recent phase I trial (PMID36997799), nivolumab IT delivery appears safe while its efficacy remains to be further investigated. **Methods:** We retrospectively reviewed melanoma patients with LMD treated with continuous IT administration of nivolumab (after decision in multidisciplinary tumor boards) at 2 institutions from February 2021 to October 2023. Patients received 10 to 13.5 mg/day of IT nivolumab delivered through a catheter (cath) connected to an implanted pump. Nivolumab concentrations were monitored in spinal CSF via an independent access port. All patients were enrolled in the MelBase cohort. **Results:** 11 patients (5 females, median age 52) were treated with continuous IT nivolumab with median (IQR) time to follow-up of 2.5 (1.1-6.3) months (m). Nivolumab was delivered through a spinal (n=10) and ventricular (n=1) cath. All patients had progressed on systemic immunotherapy (ipilimumab + nivolumab n=10, nivolumab n=1). Five patients had symptomatic LMD. All patients were ECOG 0 or 1 except one patient ECOG 3 (due to neurological deficit). Primary tumors were cutaneous (n=8), mucosal (n=1) and unknown (n=2). Tumors were BRAFV600 (n=10) and NRASQ61-mutated (n=1). All but 3 patients had stable extracranial disease. Concomitant systemic therapies were the following: corticosteroids (n=5), intravenous nivolumab (first 3 months of IT therapy) (n=1), and targeted therapies (n=4). The median duration of IT treatment was 1.5 (0.5-2.7) m. The median overall survival (OS) was 2.5 (1.1-NA) m. OS at 3, 12 and 19 m were 36.4 % (16.6-79.5), 27.3 % (10.4-71.6) and 13.6 % (10.4-71.6), respectively. Three patients had prolonged survival (19 m n=2, 12 m n=1). Treatment-related adverse events (all reversible) occurred in 5 patients: hemorrhage on cath path (n=1, grade 2), immune-mediated meningoencephalitis (n=1, grade 3), intracranial hypotension syndrome (n=3, grade 2). Steady state was obtained after 3 weeks of continuous IT infusion. Pharmacokinetics data are summarized in Table. **Conclusions:** Survival data are slightly inferior to those previously published. However 3 patients had prolonged survival (>=1 year). Median nivolumab concentrations in CSF were comparable to through plasma concentrations at steady state after 3mg/kg IV infusion. High plasma concentrations suggest rapid clearance of nivolumab from the CSF, possibly related to reverse transcytosis of immunoglobulins. Research Sponsor: None.

Median Concentrations of Nivolumab, Microgram/ml (min-max)	Plasma	Lumbar CSF
10 mg/day (n=4)	67 (32-99)	50 (37-97)
13. 5 mg/day (n=4)	126 (40-166)	64 (36-73)

9523 Poster Session

FDG-PET associations with pathological response and survival with neoadjuvant immunotherapy for melanoma.

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Background: This study sought to describe the changes seen with FDG-PET following neoadjuvant immunotherapy in melanoma patients (pts), and explore associations with pathological response and recurrence-free survival (RFS). **Methods:** Two prospective clinical trial cohorts of stage III pts with RECIST measurable nodal melanoma were included; 1) NeoTrio, 13 pts received 2 doses of preoperative pembrolizumab alone, and 2) NeoPele, 20 pts received 2 doses of pembrolizumab and 5 weeks of lenvatinib preoperatively. All pts underwent baseline and week 6 (preoperative) FDG-PET assessments and all had surgery. PET responses were evaluated based on the modified EORTC criteria. In addition to the standard categories Complete Metabolic Response (CMR), Partial Metabolic Response (PMR), Stable Metabolic Disease (SMD), and Progressive Metabolic Disease (PMD), a novel category was established, near-CMR, where the maximum standardized uptake value (SUVmax) decreased by more than 90%. PET responses were determined while blinded to the outcome data. Pathological response was determined as per INMC criteria. **Results:** 33 pts were included, 67% male, median age 65 years, 48% BRAF mutant. Pathological response, PET response and correlations are shown in the Table. All 8 (24%) pts achieving CMR or near-CMR obtained major pathologic response (MPR), while the 14 pts (42%) with PMR had variable pathological outcomes (57% MPR, 21% pPR, 21% pNR). For the 6 pts with PMD, 5 (83%) had pNR and the one pts who achieved pCR recurred with brain metastases. After a median 29.9 mo follow-up (95% CI 27.0-33.1), PET response associated with RFS; those with CMR/near CMR had 100% 24mo RFS (nil recurrences to date) while those with PMR or SMD had inferior survival (79% and 80% 24mo RFS), and those with PMD the worst outcomes (17% 24mo RFS, all pts except one have recurred) (p=0.0029). The predictive value of PET and pathology for RFS was assessed using the Cox Proportional Hazards model. 12- and 24-month RFS AUCs of PET and pathology response were similar at 81.5% (95% CI: 67.7-95.3) vs. 80.9% (95% CI: 67.8-93.9), and 83.3% (95% CI: 69.1-97.5%) vs. 80.8% (95% CI: 66.6-94.9), respectively. **Conclusions:** FDG-PET demonstrates utility in predicting pathological response and survival with neoadjuvant immunotherapy in melanoma. PET may identify pts who are not going to be pathological responders and who have the worst survival outcomes, enabling a potential switch of neoadjuvant systemic therapy. Research Sponsor: None.

		Pathological Response			
		MPR	pPR	pNR	Total
FDG-PET Response	CMR	2	0	0	2 (6%)
	near CMR	6	0	0	6 (18%)
	PMR	8	3	3	14 (42%)
	SMD	0	2	3	5 (15%)
	PMD	1	0	5	6 (18%)
	Total	17 (52%)	5 (15%)	11 (33%)	33

Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma (RELATIVITY-047): Overall survival (OS) and melanoma-specific survival (MSS) outcomes at 3 years.

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Background: NIVO + RELA as a fixed-dose combination (FDC) demonstrated a statistically significant progression-free survival (PFS) benefit vs NIVO in RELATIVITY-047 (NCT03470922), with a clinically meaningful, but not statistically significant, improvement in OS and a numerically higher objective response rate (ORR), resulting in regulatory approval of the FDC. Here we report updated descriptive analyses with 3 years of follow-up. **Methods:** Patients (pts) were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg FDC or NIVO 480 mg Q4W. PFS per RECIST v1.1 was assessed by blinded independent central review (BICR); secondary endpoints included OS and ORR per BICR. Exploratory analyses included MSS (death due to melanoma, with censoring of deaths due to other causes), CNS metastasis-free survival in specified populations, and efficacy on subsequent systemic therapy. **Results:** At database lock (19 Oct 2023), median follow-up was 33.8 months (mo; range, 0.3–64.2). NIVO + RELA continued to show a benefit vs NIVO for PFS, OS, ORR, and MSS (Table). NIVO + RELA was also favored over NIVO across the majority of key subgroups. Subsequent systemic therapy was received by 135 pts (38%) on NIVO + RELA and 141 pts (39%) on NIVO. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 78 pts (22%) on NIVO + RELA and 43 pts (12%) on NIVO; TRAEs (any grade) led to treatment discontinuation in 63 pts (18%) and 35 pts (10%), respectively. No new treatment-related deaths were reported since the last analysis. **Conclusions:** At 3 years of follow-up, NIVO + RELA continued to show a benefit vs NIVO for PFS, OS, ORR, and MSS. OS and MSS demonstrated sustained improvement, with the OS HR 95% CI upper bound < 1. Efficacy results also continued to favor NIVO + RELA vs NIVO across the majority of prespecified subgroups. Safety of NIVO + RELA remained consistent with previous reports, with no new or unexpected safety signals. CNS metastasis-free survival and efficacy outcomes on subsequent systemic therapy will be presented. Clinical trial information: NCT03470922. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, mo (95% CI)	10.2 (6.5–15.4) / 4.6 (3.5–6.5)	
HR (95% CI)	**0.79 (0.66–0.95)**	
PFS rate, % (95% CI)		
36 mo	31.8 (26.6–37.1)	26.9 (22.1–31.9)
48 mo	29.7 (24.5–35.1)	22.4 (17.6–27.6)
60 mo	27.7 (22.5–33.2)	21.6 (16.8–26.9)
Median OS, mo (95% CI)	51.0 (34.0–NR) / 34.1 (25.2–44.7)	
HR (95% CI)	**0.80 (0.66–0.99)**	
OS rate, % (95% CI)		
36 mo	54.6 (49.2–59.6)	48.0 (42.7–53.1)
48 mo	52.1 (46.6–57.2)	43.2 (37.8–48.5)
60 mo	48.7 (43.0–54.1)	39.4 (33.5–45.2)
Median MSS, mo (95% CI)	NR / 46.7 (34.1–NR)	
HR (95% CI)	**0.75 (0.60–0.94)**	
MSS rate, % (95% CI)		
36 mo	62.7 (57.2–67.7)	54.0 (48.4–59.2)
48 mo	59.8 (54.1–65.0)	49.8 (44.0–55.3)
60 mo	58.2 (52.4–63.6)	46.6 (40.1–52.7)
ORR, % (95% CI)	43.7 (38.4–49.0)	33.7 (28.8–38.9)
ORR difference (95% CI)	**9.8 (2.8–16.8)**	

Descriptive analyses; median follow-up 33.8 mo.
NR, not reached.

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Randomized phase II evaluation of nivolumab (nivo), or relatlimab (rela), or combined nivo-rela lead-in followed by nivo-rela as first line therapy for patients (pts) with advanced melanoma (mel).

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Background: A phase II study of nivo and rela was designed to evaluate the separate antitumor activity of nivo and rela vs. the combination for first-line treatment of pts with advanced mel. We report objective response rate (ORR) at week (wk) 4 and 16, progression-free survival (PFS) for pts receiving lead-in with nivo or rela vs. combination, and correlations with immune-related pathological response (irPR) at wk 4 tumor biopsy. **Methods:** Pts were randomized (1:1:1) to lead-in treatment with 1 cycle of nivo (480mg IV q4wk), rela (160mg IV q4wk), or nivo-rela followed by combination therapy in all pts. The primary endpoint was ORR to nivo-rela by RECISTv.1.1 at wk 16. Secondary endpoints included progression-free survival (PFS), ORR according to lead-in therapy at wk4, safety, and major pathological response on biopsy at 4wk (MPRbx) per Stein et al, Ann Oncol (2019). **Results:** The trial enrolled 43 advanced mel pts, median age=67 years, female=15 (35%), ECOG PS 0=34 (79%), *BRAF*mutant=18 (42%), Stage IV=35 (81%), and LDH >ULN=37 (86%). Pts were randomized to nivo=15, rela=14, and nivo-rela=14 lead-in arms. ORR at wk 4 were 3 (20%), 1 (7.1%), and 0 (0%) in nivo, rela, and nivo-rela lead-in arms, respectively. Among 41 evaluable pts who received at least one cycle of nivo-rela radiological assessment at wk16 was partial response (PR)=14 (34.2%), stable disease (SD)=15 (36.6%), and progressive disease (PD)=12 (29.3%). ORR at wk 16 were 6 (42.9%), 2 (15.4%), and 6 (42.9%) for nivo, rela, and nivo-rela lead-in arms, respectively. Median PFS for the whole cohort was 6.5 mos (95%CI 2.2-not reached [NR]), 4.7 mos, 1.8 mos, and NR in nivo, rela, and nivo-rela lead-in arms, respectively. After adjusting for BRAF status, rela lead-in was significantly associated with worse PFS (HR=3.41, 95% CI 1.11-10.4, p=0.03). Grade ≥3 treatment-related adverse events (TRAEs) were observed in 14 (32.6%) pts. & TRAEs (any grade) leading to treatment discontinuation were observed in 9 (20.9%). After 1 cycle of nivo one pt developed myocarditis leading to death without proceeding to nivo-rela. MPRbx at wk 4 was observed in 11 (31.4%) of 35 evaluable pts and were 50%, 0%, and 43% in nivo, rela, and nivo-rela lead-in arms, respectively. MPRbx was associated with wk16 radiological response (p=0.04) and improved PFS (HR=0.29, 95% CI 0.10-0.87, p=0.03). Nivo-rela resulted in increased CD8 and CD4+FOXP3- cell densities at wk4 ($p<0.01$ and p=0.03, respectively) and CD8 density at wk 4 was associated with improved PFS (p=0.02). **Conclusions:** Nivo-rela results in 34.2% ORR and median PFS of 6.5m in pts with advanced mel after lead-in nivo, rela or combination therapy. This first single agent lead-in rela evaluation demonstrated wk 4 ORR of 7%, wk 16 ORR of 15.4% and median PFS 1.8 mos. MPRBx and CD8 density at wk4 are associated with improved PFS. Clinical trial information: NCT03743766. Research Sponsor: BMS.

A phase I dose escalation trial of BCD-145 in patients with unresectable or metastatic melanoma.

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Background: BCD-145 (nurulimab) is a fully human IgG1 mAb with modified Fc-fragment (the 1st Gln is replaced by Glu in the heavy chain sequence, and there is no terminal dipeptide composed by Gly and Lys residues) that binds to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and blocks the interaction between CTLA-4 and its ligands. This allows to stimulate T-cell proliferation, cytokine production and induces antitumor immune response. Here we present the results of multicenter open-label single-arm multi-cohort phase I trial of pharmacokinetics (PK), pharmacodynamics (PD), safety, and immunogenicity of BCD-145 in pts with unresectable/metastatic melanoma (unr/mM). **Methods:** BCD-145 monotherapy in 3+3 dose escalation [0.1, 0.3, 1, 3, 10 mg/kg intravenously Q3W] was given to 15 pts with unr/mM with measurable disease, who had failed prior therapy, ECOG 0-2. Pts with brain mts, previous therapy with aCTLA-4 and/or aPD-1/PD-L1 drugs were not allowed. The main objective of the study was to evaluate PK, PD, tolerability, immunogenicity, safety, dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) identification. Secondary objectives included tumor response rate (irRECIST). **Results:** BCD-145 proved safety and overall was well tolerated. DLT and MTD were not reached. Any grade (Gr) adverse events (AEs) occurred in 100% (15/15) of pts. 33.3% (5/15) of pts had AE/SAE of Gr 3-4, including hypertension Gr 3 (1 at 1 mg/kg), hypercalcemia Gr 4 (2 at 1 mg/kg), hypokalemia Gr 3 (2 at 1 mg/kg), neutropenia Gr 3 (1 at 0.3 mg/kg), anemia Gr 3 (1 at 1 mg/kg), lung infection Gr 3 with hospitalization (1 at 1 mg/kg). Only 2 pts had a treatment-related AE Gr 3-4. Immuno-related AE were identified in 46.7% (7/15), manifested by symptoms of thyroiditis (mainly Gr 1) and diarrhea Gr 2 (1 at 10 mg/kg). There was 1 death (at 1 mg/kg) due to progression. There is dose-dependent peak study drug serum concentrations and systemic exposure. Two dosage regimens (1 mg/kg, 3 mg/kg Q3W) allowed to achieve the optimal concentration. BCD-145 increased subpopulations of activated HLA-DR+ CD4+ and CD8+ T lymphocytes, CD4+ICOS+ T-lymphocytes, absolute lymphocyte counts in all cohorts without significant differences. Binding and neutralizing Abs against BCD-145 were detected in 2 pts from different dose cohorts (0.3 mg/kg, 1 mg/kg). PR and SD were registered in 2 pts of each response group. 30.8% of pts achieved disease control, which is consistent with published data on other CTLA-4 inhibitors. A dose of 1 mg/kg is determined as recommended phase 2 dose (RP2D). **Conclusions:** BCD-145 demonstrated a tolerable safety profile and preliminary anti-tumor activity in pts with unr/mM. Anti-tumor effects of BCD-145 were observed in pts who had progressed on prior treatment. Further co-targeting PD-1 and CTLA-4 simultaneously will achieve a better anti-tumor activity due to cooperative binding to exhausted T-cell subsets. Clinical trial information: NCT03472027. Research Sponsor: JCS BIOCAD.

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A phase I/II study of KD6001, a novel fully human anti-CTLA4 IgG1 monoclonal antibody, in combination with toripalimab in patients with advanced melanoma.

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Background: Anti-CTLA4 and anti-PD-1 immunotherapies have changed the treatment landscape of patients (pts) with advanced or metastatic melanoma. However, there is still a need to develop an anti-CTLA-4 antibody with further improved safety and efficacy profile. KD6001, a novel fully human anti-CTLA4 IgG1 monoclonal antibody that exhibits immunomodulatory effects, enhances T-cell-mediated anti-tumor immune response, and shows preliminary anti-tumor activity as monotherapy in a FIH phase I trial in pts with advanced solid tumors. Here we report a new study result of KD6001 in combination with toripalimab, an anti-PD-1 monoclonal antibody, in pts with advanced melanoma (KD6001CT02). **Methods:** KD6001CT02 is a phase I/II study conducted in advanced melanoma. This study consists of dose escalation and dose expansion phases. The primary objective is to evaluate the safety and tolerability of KD6001 in combination with toripalimab and determine the MTD/RP2D. The secondary objectives are to measure antitumor activity, immunogenicity, and pharmacokinetics (PK). **Results:** As of 15 Dec 2023, 29 pts with melanoma were enrolled (dose escalation n=6 and dose expansion n=23), including 9 (31.0%) acral, 9 (31.0%) nonacral cutaneous, 8 (27.6%) mucosal, and 3 (10.3%) unknown primary subtypes. 18 of them had no brain metastases. The median age was 56 yrs (range 41-78 yrs). The majority of pts previously received anti-PD-1/L1 therapy (16/29, 55.2%) and 27.6% of them received ≥3 lines of therapy. No dose-limiting toxicity or ≥Gr 3 adverse events (AEs) were reported in the dose escalation phase. The study did not reach MTD. 26 (89.7%) pts had treatment-related adverse events (TRAEs), with ≥Gr 3 TRAEs occurring in 3 (10.3%) pts and were well manageable. All other TRAEs were Gr 1 or 2. There were no death events due to TRAEs. No novel safety signals were seen other than the previously reported safety profile of treatment with a combined inhibition of CTLA-4 and PD-1. At data cutoff, among 13 efficacy-evaluable pts without brain metastases, the unconfirmed and confirmed objective response rates (ORR) were 38.5% and 23.1%, respectively. The disease control rate (DCR) was 76.9%. Among 3 pts with confirmed partial response (PR) , 2 pts were mucosal melanoma and 1 patient was nonacral cutaneous melanoma. Among 7 pts who received KD6001 as the ≥2 line treatment and all failed anti-PD-1/L1 therapy, the unconfirmed and confirmed ORR were 57.1% and 42.9%, respectively. DCR was 85.7%. The median PFS and OS were not reached. **Conclusions:** KD6001 in combination with toripalimab for treatment of advanced melanoma was safe, well-tolerated and showed anti-tumor activity in pts with advanced melanoma. Preliminary analysis indicates that KD6001 combined with toripalimab is efficacious in pts who have progressed after previous anti-PD-1/L1 therapy and in pts with mucosal melanoma. Clinical trial information: NCT05723432. Research Sponsor: Shanghai Kanda Biotechnology Co., Ltd.

9528 Poster Session

Efficacy of encorafenib/binimetinib in patients with metastatic melanoma with brain metastases: Results from the nationwide Dutch Melanoma Treatment Registry.

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Background: Data on the effectiveness of encorafenib plus binimetinib in patients with melanoma brain metastases (BMs) are lacking. Therefore, we aimed to investigate the effectiveness of encorafenib/binimetinib treatment in melanoma patients with BMs. **Methods:** All melanoma patients with BMs treated with encorafenib/binimetinib between 2019 and 2023 in the Netherlands were included from the nationwide Dutch Melanoma Treatment Registry. Patients with prior BRAF/MEK inhibition treatment were excluded. We analyzed overall response rates (ORR), progression-free (PFS), and overall survival (OS) from start of encorafenib/binimetinib. We performed subgroup analysis for symptomatic versus asymptomatic BMs and previous treatment versus no previous treatment. **Results:** In total, 208 patients were included. Median age was 61 years and 58.2% of the patients was male. Lactate dehydrogenase levels were elevated in 48.1% of the patients and symptomatic BMs were present in 63.5%. Of all patients, 41.8% received prior immunotherapy and for 58.2% encorafenib/binimetinib was the first-line treatment. The median follow-up duration was 23.2 months. The ORR was 67.3%. Median PFS was 5.6 months (95% confidence interval (CI): 4.9-6.2) and median OS was 10.9 months (95% CI: 9.6-14.0). OS was significantly shorter in patients with symptomatic BMs versus asymptomatic BMs (median 9.7 versus 22.9 months, $p<0.01$), while PFS was similar (median 5.6 versus 5.8 months, $p=0.07$). Previously untreated patients had worse prognostic characteristics than previously treated patients. PFS was not significantly different between patients with versus without previous systemic treatment (median 8.8 versus 5.2 months, $p=0.08$), while OS from start of encorafenib/binimetinib was longer for previously treated patients (median 15.9 versus 9.6 months, $p<0.01$). **Conclusions:** Encorafenib plus binimetinib has clinical activity in real world melanoma patients with BMs, but PFS and OS are shorter than previously reported for patients without brain metastases. These data may aid physicians in clinical decision-making. Research Sponsor: None.

9529 Poster Session

Comparison of clinical outcomes of stable disease with confirmed tumor reduction and RECIST partial response for tebentafusp in metastatic uveal melanoma (mUM).

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Background: Tebentafusp (gp100 x CD3) has demonstrated an overall survival (OS) benefit in mUM. Benefit was observed in patients (pts) who achieved a RECIST v1.1 partial response (PR), stable disease (SD) and even progressive disease (PD) (Nathan 2021). In Phase (Ph) 1, some melanoma pts had SD with tumor reduction > 10% that was confirmed at ≥ 1 subsequent scan (referred to as minor response, MR). In Ph 2, an analysis of MR was pre-specified as an endpoint and presented here. **Methods:** 127 HLA-A*02:01+ pts with previously treated mUM received weekly intravenous tebentafusp following intra-pt dose escalation of 20mcg Week 1, 30mcg Week 2 and 68mcg Week 3+ (NCT02570308; Carvajal 2022). Radiologic assessments were performed every 8 weeks until week 40, then q12 weeks. Tumor assessment was evaluated by a blinded independent review committee per RECISTv1.1. MR was prospectively defined as RECISTv1.1 best response of SD with reduction in sum of target lesions of -10% to -29% and which was confirmed ≥ 4 weeks later. ctDNA levels were assessed using a targeted mPCR-NGS assay for mutations in 15 genes including mUM oncogenes GNAQ, GNA11, SF3B1, CYSLTR2, PLCB4 and EIF1AX (Natera). Molecular response was defined as ≥ 0.5 log [68%] ctDNA reduction by week 9. Data cut off: Oct 2022. Median duration of follow-up was 46 months. **Results:** Of 127 pts, the clinical benefit rate of PR + SD was 50% (64/127). 25% (32/127) had any tumor reduction that was confirmed on ≥ 1 subsequent scan, including 6 PR (ORR 5%) and 26 SD (20%). 8/26 SD (6% of 127) met the pre-defined threshold for MR, most (5/8) had >20% reduction. The median duration of response for PR and MR were 8.7 months and 10.6 months, respectively. The estimated percent of pts with PR and MR remaining in response at Month 20 were 20% and 33%, respectively. 3/6 PR pts were alive ≥ 3 years vs 3/8. 58% of PR + SD pts with evaluable ctDNA had a molecular response (26/45), including 2/4 PRs and 5/5 MRs. **Conclusions:** This Ph2 UM study prospectively confirmed that a subset of SD patients had tumor reduction over multiple scans. The frequency of minor response was similar to that of PR and had similar durability, OS and ctDNA molecular response. SD with confirmed tumor reduction is an emerging endpoint for the ImmTAC platform and will be studied in other trials (NCT05549297, NCT04262466). Clinical trial information: NCT02570308. Research Sponsor: Immunocore.

9530 Poster Session

The 31-GEP to identify patients with localized cutaneous melanoma at the highest risk of metastasis to the central nervous system.

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Background: Cutaneous melanoma (CM) metastasis to the central nervous system (CNS) has a poor prognosis; however, treatment of CNS metastasis while asymptomatic is associated with better outcomes. CNS imaging is not routinely recommended for patients with early-stage CM (i.e., AJCC stage I–II), yet ~14% of patients with stage II melanoma will develop CNS metastases. The 31-gene expression profile test (31-GEP) identifies patients at a low (Class 1A), intermediate (Class 1B/2A), or high risk (Class 2B) of tumor recurrence and metastasis. We evaluated the association of CNS metastasis with the 31-GEP test result for the purpose of directing CNS-directed imaging to detect metastasis earlier and, thus, improve outcomes. **Methods:** A retrospective analysis of patients clinically tested with the 31-GEP from 2013-2017. Patients were included in the study if they had clinical or pathological AJCC stage I-II CM (n=1,662). Kaplan-Meier analysis was used to estimate 5-year recurrence-free survival (RFS), and the log-rank test was used to compare survival between groups. Patients with non-CNS metastasis were censored at the time of recurrence. Univariate analysis to identify predictors of CNS metastasis was performed for tumor location, mitotic rate, Breslow thickness, ulceration status, tumor-infiltrating lymphocytes, age, sex, regression, lymphovascular invasion, tumor subtype, and 31-GEP results. Only significant ($p<0.01$) factors in univariate analysis were included in Cox multivariable analysis. **Results:** Median follow-up time was 4.6 years (range: 0.02-14.5 years). Patients with a CNS metastasis tended to have thicker tumors (median 1.1 vs. 0.8, p=0.003), higher mitotic rate/mm2 (median 2.5 vs. 1.0, $p<0.001$) and a higher proportion of males (73% vs. 55%, p=0.03) than patients that did not develop CNS metastasis. Patients with a Class 2B result were significantly more likely to develop CNS metastasis (7.4% [15/202]) relative to patients with a Class 1B/2A (1.7% [5/291]) or Class 1A (0.9% [10/1,169], $p<0.001$) 31-GEP result. Patients with a Class 2B result had significantly lower 5-year RFS than patients with a Class 1B/2A or Class 1A result (91.6% vs. 98.2% vs. 99.1%, $p<0.001$) and had shorter times to CNS metastases (1.5 yrs. vs. 4.2 yrs. vs. 3.4 yrs. $p<0.001$). In multivariable analysis, only the 31-GEP Class 2B (HR=9.42, $p<0.001$) result was a significant predictor of CNS metastasis; mitotic rate, Breslow thickness, and ulceration were not significantly predictive. **Conclusions:** Under multivariable analysis, the 31-GEP was the only significant predictor of CNS metastasis, and CNS metastasis occurred early (1.5 yrs). Patients with early-stage I-II CM and a Class 2B result should be considered for CNS imaging to enable asymptomatic detection of CNS metastasis and, thus, improve survival relative to symptomatic CNS metastasis. Research Sponsor: Castle Biosciences, Inc.

Length of treatment after partial or complete remission in immunotherapy for metastatic melanoma: An EUMelaReg real world study.

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Background: A significant proportion of patients (pts) with non-resectable melanoma treated with immune checkpoint inhibitors (ICI) achieve durable remissions, but there is limited data on the optimal duration of ICI therapy in these pts. Therefore, the influence of the duration and maintenance of ICI therapy in pts with a partial (PR) or complete remission (CR) on further outcome was investigated. **Methods:** Primary objectives was the survival outcome after achieving PR or CR in non-resectable stage III/IV melanoma in relation to baseline prognostic variables and duration of maintenance treatment with ICIs in 1st line. This retrospective study evaluated melanoma cases from the EUMelaReg treatment registry, who achieved a best overall response (BOR) of PR or CR with either single agent anti-PD1 or combined anti-PD1/anti-CTLA4 in 1st line. Cases were stratified according to treatment duration after achieving a PR or CR: < 6 months (M), 6-12 M, > 12 M. To address immortal time bias, cases with early progression were cloned into all respectively compatible strata. These synthetical strata were further analyzed and compared by propensity score weighting, and robust confidence intervals were retrieved by bootstrapping techniques. **Results:** A total of 1,291 pts were included in the analysis. After cloning, 2,144 cases could be stratified to the synthetical arms of <6 M (26.5%), 6-12 M (31.4%) or >12 M (42.1%) treatment continuation after achieving PR or CR. Adjusted Kaplan-Meier estimates showed that treatment until progressive disease (PD) or > 12 M after remission resulted in prolonged progression-free (PFS) and overall survival (OS) compared to the < 6 M arm (hazard ratio (HR): 0.82 [95% confidence interval (CI): 0.6-0.9] and HR: 0.67 [95% CI: 0.5-0.9], respectively).This effect was more pronounced in PR (HR 0.66 for OS) than in (HR 0.84 for OS). Treatment for 6-12 M compared to < 6 M also showed a trend towards prolonged PFS and OS (HR: 0.85 [95% CI: 0.7-1.1] and HR: 0.82 [95% CI: 0.6-1.1], respectively). **Conclusions:** This study showed PFS and OS benefit for pts continuing on treatment for > 12 M or until progression after achieving PR or CR compared to pts treated for < 6 M. Research Sponsor: None.

	n	PFS* HR (95% CI)	OS* HR (95% CI)	Median Follow-up* [M] (95% CI)
Actual duration of treatments	1,291			
Maintenance tx < 6 M	567	Ref	Ref	28.3 (25.2-33.5)
Maintenance tx 6-12 M	338	0.64 (0.51-0.79)	0.58 (0.44-0.78)	25.8 (24.0-27.8)
Maintenance tx >12 M	386	0.38 (0.30-0.48)	0.28 (0.21-0.41)	24.4 (20.5-27.9)
	↓ **cloning for immortal time bias** ↓			
Synthetic population**	2,144			
Maintenance tx < 6 M	567	Ref	Ref	28.3 (23.8-34.8)
Maintenance tx 6-12 M	674	0.85 (0.68-1.07)	0.82 (0.59-1.07)	24.5 (20.1-29.2)
Maintenance tx >12 M	903	0.72 (0.57-0.91)	0.67 (0.49-0.92)	25.8 (23.5-28.7)

*All survival times were calculated from time of BOR.
**Cases with early progression were cloned into all strata compatible with a respective maintenance treatment category.

9532 Poster Session

Long-term overall survival after isolated liver perfusion with melphalan in patients with isolated liver metastases of uveal melanoma (SCANDIUM trial).

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Background: Uveal melanoma is a rare subtype of melanoma characterized by frequent metastases to the liver. The median survival for patients with liver metastases is less than one year, and there are few systemic treatment options available, providing only small survival benefits. Patients with liver metastases of uveal melanoma were in the SCANDIUM trial randomized to a one-time treatment with isolated hepatic perfusion (IHP) with high dose melphalan and investigator´s choice. We have previously reported that IHP gave significantly superior response rates and progression-free survival compared to best alternative care Furthermore, the primary endpoint, overall survival (OS) rate at 24 months was numerically higher for the IHP treated group (46.5% vs 29.5%), but the difference was not statistically significant. Here we present extended OS follow-up. **Methods:** In this randomized, controlled, phase III trial, treatment naïve Swedish patients with isolated liver metastases from uveal melanoma were between 2013 and 2021 randomly assigned in a 1:1 ratio to receive a one-time treatment with IHP or best alternative care (control group). No crossover from the control group to the IHP group was allowed. **Results:** A total of 87 patients were randomized and assigned to either IHP (43 patients) or control (44 patients). In the IHP group, 41 (89%) patients received IHP. In the control group, the first-line treatment was chemotherapy (49%), immunotherapy (39%) or localized treatment interventions (9%). The overall response rate was 40% in the IHP group, with a median duration of response of 13.7 months (95% CI, 11.6-18.3, n=17). At a minimum follow-up of 36 months, the 3-year OS rate was 18.6% (95% CI, 10.0-34.8%) in the IHP group compared to 9.1% (95% CI, 3.6-23.1%) in the control group (p=0.23, fisher exact test), and the 5-year OS rate was 16.3% (95% CI, 8.3-32.1%) compared to 6.8% (95% CI, 2.3-20.3%). The median OS in the IHP group was 21.4 months (95% CI, 19.0-30.4 months) compared to 17.3 months (95% CI, 13.8-22.3 months) in the control group (p=0.11, log-rank test). **Conclusions:** This extended analysis from the SCANDIUM trial supports long-term efficacy of a one-time treatment with IHP compared to best alternative care in patients with isolated liver metastases of uveal melanoma. Clinical trial information: NCT01785316. Research Sponsor: Sahlgrenska University Hospital; The Assar Gabrielsson Foundation; Gothenburg Society of Medicine; Wilhelm and Martina Lundgrens Foundation; Knut and Alice Wallenberg Foundation; Wallenberg Centre for Molecular and Translational Medicine.

Overall survival after isolated hepatic perfusion in combination with ipilimumab and nivolumab in patients with uveal melanoma metastases (the SCANDIUM II trial).

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Background: Uveal melanoma (UM) is a rare disease, that commonly metastases to the liver metastases and has a very poor prognosis. In patients with metastatic UM to the liver, a one-time 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) (IPI3/NIVO1) has shown response rates of 11-18%. The impact of these treatments on overall survival (OS), if combined, is unclear. In the SCANDIUM II trial, we investigated the safety and tolerability of combination of IHP and IPI3/NIVO1. **Methods:** In this multicenter open, randomized, controlled, phase Ib trial, patients with liver dominant metastatic uveal melanoma were randomized to receive either IHP followed by combination immunotherapy (four cycles IPI3/NIVO1) (Arm A) or one cycle of IPI3/NIVO1 before IHP followed by three cycles IPI3/NIVO1 (Arm B). Thereafter, patients in both Arm A and B received monotherapy with nivolumab (480 mg q4w) for up to 1 year. Isolated hepatic perfusion 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. **Results:** In total, 18 patients were included in the trial, 9 randomized to Arm A and 9 to Arm B. 78% were treatment naïve; 28% had both hepatic and extra-hepatic metastases. Three patients did not undergo IHP as planned, one in arm A and two in arm B. Patients received a mean of 2.4 cycles of IPI/NIVO in Arm A and 3.0 cycles in Arm B. There were more IPI/NIVO related adverse events (grade I-IV) in arm B (48 vs. 86). The overall response rate was 38%, 57% in arm A and 22% in arm B, and the median duration of response was 11.9 months (95% CI, 8.2-NE, n = 6). At a minimum follow-up of 18 months, the overall survival rate was 50% (95% CI, 31.5-79.4%) in the whole study population, 56% (95% CI, 31-99%) in arm A and 44% (95% CI, 21-92%) in arm B. The median OS in arm A was 18.2 months (95% CI, 13.2-NA months) and 17.2 months (95% CI, 14.0-NA months) in arm B. The primary endpoint of adverse events has been reported previously. **Conclusions:** In patients with liver dominant metastatic uveal melanoma, combining IHP with IPI3/NIVO1 is a feasible treatment. One dose of IPI3/NIVO1 before IHP had no obvious benefit in response or OS, but was associated with higher rates of toxicity. There was no apparent survival advantage compared to patients in the SCANDIUM trial with IHP only, however, sample size and non-overlapping patient characteristics severely hamper comparison between the trials. The numerically higher response rate in Arm A warrants a larger randomized study that is designed to detect a difference between IPI/NIVO with or without IHP. Clinical trial information: NCT01785316. 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.

9534 Poster Session

EVICTION study: ICT01, an anti-Butyrophilin 3A monoclonal antibody activating γ9δ2 T cells in combination with pembrolizumab in checkpoint inhibitor refractory melanoma.

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Background: γ9δ2 T-cell tumor infiltration is associated with a favorable prognosis making these cells a new potential target for immunotherapy. The anti-BTN3A mAb ICT01 selectively activates γ9δ2 T cells and is being studied in the phase1/2a EVICTION Trial (NCT04243499). In preclinical studies, ICT01 induces upregulation of PD-1 on γ9δ2 T-cells and combination with pembrolizumab leads to enhanced cancer cell killing, providing scientific rationale to evaluate this combination. Here we present interim results from EVICTION of ICT01 in combination with pembrolizumab in patients with checkpoint inhibitor (CPI) refractory melanoma. **Methods:** EVICTION evaluated ICT01 (20 μg to 200 mg, Q3W) plus pembrolizumab (200mg IV Q3W) in a dose escalation solid tumor basket design that resulted in an ongoing expansion cohort of patients with CPI refractory melanoma (2 dose levels, 7 and 200 mg ICT01). Patients are selected based on higher baseline γ9δ2 T cells. Efficacy evaluations by i/RECIST 1.1 are conducted every 8 weeks. Disease Control Rate (DCR) as primary efficacy endpoint is defined as the sum of complete response (CR), partial response (PR) and stable disease (SD, minimum week 16). Baseline and on-treatment blood and biopsy specimens are collected for correlative translational work. **Results:** ICT01 plus pembrolizumab has a favorable safety profile with first-dose Grade 1/2 infusion related reactions (IRR) and cytokine release syndrome (CRS) as most common adverse events (in 38% and 19% of patients respectively, 5%and 2% Grade 3) among all doses and indications. To date, 35 CPI refractory melanoma patients have been enrolled, of which 65% have received 2+ prior lines of CPI. Currently 21 patients are evaluable at week 16 with a DCR of 42% (including 3 PR) and a 6-month progression free survival of 38%. In the circulation, full BTN3A receptor occupancy on immune cells was achieved at 7 mg dose, with down-modulation of BTN3A observed at doses greater than 20 mg. Clinical response was related to baseline tumoral BTN3A expression, sustained elevation of IFNg levels, and tumor microenvironment remodeling, including increased PD-L1 expression and CD8 T cells proliferation and activation. **Conclusions:** ICT01 in combination with pembrolizumab has a favorable safety profile and promising efficacy data. Patient selection based on BTN3A tumor expression will be further evaluated as an enrichment strategy. Clinical trial information: NCT04243499. Research Sponsor: None.

9535 Poster Session

A DNA plasmid melanoma cancer vaccine, SCIB1, combined with nivolumab + ipilimumab in patients with advanced unresectable melanoma: Efficacy and safety results from the open-label phase 2 SCOPE trial.

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Background: Targeting melanoma by T cells drives anti-tumor responses. We previously showed that SCIB1, a DNA vaccine incorporating T cell epitopes from TRP-2/gp100 into an antibody framework to allow Fc targeting of activated dendritic cells, was successful as monotherapy in a Phase 1/2 trial in Stage III/IV melanoma patients. Disease control was achieved in 60% of cases of unresectable melanoma. In addition, 88% of 20 Stage III/IV patients treated with SCIB1 who had had a previous successful tumor resection, were disease free for 5 years. 1st line combination treatment with nivolumab and ipilimumab in advanced melanoma has a reported ORR of 50%. The current SCOPE trial tests the hypothesis that patients with unresectable melanoma may improve response rate when SCIB1 is given with checkpoint inhibitors (CPI). **Methods:** Previously untreated patients with unresectable Stage III/IV melanoma were treated with nivolumab with ipilimumab and SCIB1 (8 mg) i.m. using needle-free injections at a fixed dosing schedule for a total of 10 doses over 24 months. The CPI therapy was administered in accordance with respective SmPC. ORR, as measured by RECIST 1.1 in the intention-to-treat population, is the primary endpoint. The study is designed using Simon's two stage methodology with 80% power when the ORR of no interest is 50% and the true ORR is 70% with an overall type I error of 5%. In the 1st stage, 15 patients have been enrolled and as there were more than 8 clinical responses (ORR [CR or PR]) within 25 weeks of the 1st SCIB1 dose. Having passed Simon Stage 1, further recruitment continues. The null hypothesis will be rejected if 27 or more responses are observed in 43 patients. **Results:** To date, 23 patients have received the combination of SCIB1 with nivolumab and ipilimumab. At study entry, all patients were Stage IV. 13 patients have reached the first imaging timepoint at 13 weeks, the objective response rate is 11/13 (85%). 11/11 responses were confirmed in a subsequent scan (1 CR and 10 PRs); DCR 12/13 (92%) and 1 PD. Patients showed a 40-100% reduction in tumor volume at 13 and/or 25 weeks. Most of the SCIB1 adverse reactions were Grade 1/2 injection site related or headaches. 3 patients reported Grade 3 events (rash, neutropenia and raised GGT) all related to the CPIs. Observed toxicity frequency and intensity was in line with reported figures from ipilimumab/nivolumab therapy. Serious adverse reactions to date have all been related only to the CPIs. **Conclusions:** SCIB1 given with nivolumab and ipilimumab, as 1st line treatment in unresectable melanoma, improved the ORR to 85% without an increase in clinically meaningful adverse events. These results, if confirmed in the larger ongoing patient cohort, provide confidence in initiating a randomized registration program in unresectable melanoma patients with this novel DNA plasmid technology. Clinical trial information: NCT04079166. Research Sponsor: Scancell Limited.

9536 Poster Session

Use of baseline and serial ctDNA dynamics to predict outcomes in patients treated with first-line tebentafusp, including those who were and were not treated beyond progression.

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Background: Tebentafusp (tebe), a bispecific soluble T cell receptor specific for a gp100 peptide, is licensed for the treatment of metastatic uveal melanoma (mUM) in HLA-A*02:01+ individuals. As part of the pivotal, Phase 3 IMCgp100-202 study, 378 mUM pts were randomized to receive tebe or investigators choice. Approximately 60% of patients (pts) with metastatic UM in the IMCgp100-202 study had detectable baseline ctDNA. We have reported the strong relationship between change in ctDNA at 9 weeks (wks) and overall survival (OS). Additionally, radiographic treatment response is a poor predictor of who is benefitting from therapy. We hypothesized that ctDNA dynamics would help identify those patients (pts) who benefit from treatment beyond progression (TBP). **Methods:** Sera (n=202 pts) collected at baseline and wk 9 on tebe were analyzed for ctDNA using a targeted mPCR-NGS assay for 15 genes including GNAQ, GNA11, SF3B1, PLBC4, EIF1AX, and CYSLTR2. RECISTv1.1 was assessed by investigators; TBP was allowed per protocol. OS was analyzed in subsets of pts who were not TBP, and those who were TBP and treated with tebe for $<$ or $>$ 16 wks; the approximate time point where TBP pts would have had confirmatory imaging, although confirmatory scan data is not available. At baseline, pts were determined to be ctDNA detectable or undetectable. At wk 9, pts were determined to have cleared ctDNA, $<$ or $\geq$ 68% (0.5 log-fold) reduction, $<$ or $\geq$ 50% reduction. Data cut-off was July 2023. **Results:** Of 202 pts randomized to tebe and with ctDNA at baseline and wk 9, 126 (62%) received TBP (80 $<$16 wks, 46 $\geq$ 16 wks). Undetectable ctDNA at baseline was associated with improved OS regardless of TBP, while TBP was associated with improved OS in those with baseline detectable ctDNA (hazard ratio, HR, 0.59, 95% confidence interval, CI, 0.4-0.88). Subgroup analysis of those with baseline detectable ctDNA demonstrated improved OS in only those who received TBP for $\geq$ 16 wks (HR 0.33; 95% CI 0.21-0.51). Clearance of ctDNA at wk 9 was associated with better OS than in those who did not have clearance. TBP was associated with better OS in pts who did not have clearance (HR 0.48, 95% CI 0.30-0.79), but not in those with clearance (HR 0.87, 95% CI 0.43-1.78). Finally, TBP was associated with improved outcomes in pts with $\geq$50% and $\geq$68% reduction, compared to those without reduction, HR 0.63 (95% CI 0.4-0.97) and 0.62 (95% CI 0.39-0.99), respectively. **Conclusions:** Baseline and wk 9 ctDNA detection predicts OS in mUM pts treated with first line tebe. The utility of ctDNA predicting pts most likely to benefit from TBP is less clear, although TBP seems to be more beneficial in those with reduction of ctDNA at wk 9. Optimization of time points, assay, and integration of ctDNA data with radiomics are necessary to understand the true utility of ctDNA in helping select which pts should receive TBP. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

Association between clinical and disease characteristics and detectable or undetectable baseline ctDNA in patients with metastatic uveal melanoma.

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Background: Tebentafusp, a bispecific soluble TCR specific for a gp100 peptide, is licensed for the treatment of metastatic uveal melanoma (mUM) in HLA-A*02:01+ individuals. 82% of patients (pts) with mUM in the IMCgp100-102 (previously treated; 2L+) and 61% in IMCgp100-202 (frontline; 1L) studies, respectively, had detectable baseline ctDNA. There is a strong relationship between decrease in ctDNA by 9 weeks and overall survival (OS) [Carvajal 2022; Hassel & Piperno-Neumann 2023]. Patients with undetectable baseline ctDNA had improved survival despite having macroscopic disease. In this study, we report the characteristics of baseline ctDNA undetectable vs detectable disease. **Methods:** Disease characteristics of 202 1L (Study 202) and 117 2L+ (Study 102) pts who had baseline undetectable or detectable ctDNA (unDNA vs detDNA) were compared in a post-hoc unplanned analysis. ctDNA detection was analysed at baseline and up to week 9 on tebentafusp using targeted mPCR-NGS assay for mutations in 15 genes including GNAQ, GNA11, SF3B1, CYSLTR2, PLCB4 and EIF1AX. Largest lesion size groups ($\leq$ 3 cm, 3-8 cm, $>$ 8 cm) were defined by American Joint Committee on Cancer 7th Ed. Presence of oncogenic mutations in GNAQ, GNA11, SF3B1 and BAP1 were assessed by WES on metastatic tissue biopsies. **Results:** Baseline ctDNA levels increased in association with size of largest lesion regardless of number of prior therapies. However, there was an association between disease burden (defined by largest lesion size) and unDNA vs detDNA in both studies, with all pts with largest liver lesion $>$ 8 cm having detDNA. In Study 202, % of the population with unDNA vs detDNA was 50% vs 50% for $\leq$ 3cm and 27% vs 73% for 3.1-8 cm. While OS was similar for unDNA & detDNA in pts with $\leq$ 3cm lesions, OS was longer for pts with unDNA vs detDNA who had baseline tumor size 3.1-8 cm in both studies (Table). Within this 3.1-8 cm group, pts with unDNA tended to have lower LDH, AST, and ALP. Initial analysis showed no difference in the frequency of GNAQ, GNA11, SF3B1 or BAP1 mutations between unDNA and detDNA groups. Further data on somatic mutation defined groups and RNAseq gene expression in unDNA and detDNA groups will be presented. **Conclusions:** Patients with unDNA were more likely to have smaller disease burden than those with detDNA; however, many pts with unDNA had a significant burden of metastatic disease. Baseline unDNA was associated with improved OS outcome vs detDNA in pts with 3.1-8 cm baseline metastatic deposits, but not in pts with $\leq$ 3cm disease. No association was seen between oncogenic background of GNAQ/GNA11/SF3B1/BAP1 and unDNA vs detDNA. Clinical trial information: NCT02570308; NCT03070392. Research Sponsor: Immunocore.

	Study 202 Median OS (95% CI)		Study 102 Median OS (95% CI)	
Lesion Size	**unDNA**	**detDNA**	**unDNA**	**detDNA**
≤3 cm	28.7 (24.3-41.1)	30.4 (22.5-38.2)	39.5 (6.37-NA)	21.3 (13.3-28.5)
3.1-8cm	20.9 (15.9-NA)	12.2 (10.4-14.8)	34.2 (12.8-NA)	13.11 (9.8-17.4)

9538 Poster Session

Interleukin-6 receptor blockade with tocilizumab to reduce immune-related toxicity with ipilimumab and nivolumab in metastatic melanoma.

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Background: Interleukin-6(IL-6) blockade has reversed steroid-refractory immune-related toxicity in patients receiving immune checkpoint blockade (ICB). IL-6 and its downstream acute phase reactants are also associated with short survival and therapeutic resistance in patients receiving single agent or combination ICB. We undertook a phase II trial of IPI, NIVO and the IL-6 receptor blocking antibody tocilizumab (TOCI) in unresectable melanoma. **Methods:** In a phase II, Simon-design two-stage trial, 70 patients with untreated metastatic melanoma received IPI at 1 mg/kg and NIVO at 3 mg/kg for 4 induction doses to week 12, and TOCI at 4 mg/kg every 6 weeks up to week 24. Maintenance NIVO was administered at 240 mg intravenously (IV) from weeks 12 to 24, then at a dose of 480 mg IV every 4 weeks for up to 2 years of treatment. To proceed past the first stage of 18 patients, 12/18 RECIST responses or more and/or a grade 3-5 treatment related immune-related adverse event (irAE) rate of $\leq$5/18 were required. Those criteria were both fulfilled, and in the second stage 49 patients were treated, with 3 additional patients accrued. Serum and peripheral blood samples were collected for biomarker assays at baseline and week 7. **Results:** There were 40/70 RECIST responders with a 57% best overall response rate (BORR), (exact 95% confidence interval (CI) of 44-68%) of partial response (PR) or complete response (CR); 6 patients had stable disease (SD), 24 with progression, at a median of 2.4 years of follow-up. A total of 46 patients had clinical benefit (CR+PR+SD) = 65% (exact 95% CI 37-81%). Median progression-free survival was 13 months. The expected BORR was 47% in the randomized Checkmate-511 trial at the same doses of IPI/NIVO. There have been 16 cases of grades 3-4 irAE including 3 episodes of colitis for a total of 16/71 patients eligible for toxicity = 22% (exact 95% CI: 12-31%), all grade 3/4; the expected rate of grades 3-5 TRAEs was 34% per Checkmate-511. The rate of irAE leading to discontinuation was 14%; it was 25% for CheckMate 511. Twenty-one deaths (30%) occurred, all due to progression. All grade 3-4 irAES were reversible and no grade 5 toxicity was seen. Osteopontin^{+}IL6^{+}C-D45RA^{neg}classical monocytes were associated with response, and higher levels of naive CD8 T cells were associated with progression. CD16^{+}CD56^{+}CD57^{+} mature natural killer cells were significantly lower in patients with grade 3-4 immune-related toxicity. **Conclusions:** Prophylactic TOCI resulted in a low rate of grade 3-4 irAEs by week 24 in patients with stage IV melanoma receiving induction IPI 1 mg/kg and NIVO 3 mg/kg while maintaining a favorable overall response rate and survival. Novel biomarkers of response and toxicity including NK cells and monocytes as well as naïve and effector memory CD8 T cells were defined by high-resolution flow cytometry. Additional correlative data will be presented. Clinical trial information: NCT03999749. Research Sponsor: BMS; National Cancer Institute.

First-line treatment preferences for advanced melanoma among oncologists and patients in the US: A discrete choice experiment.

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Background: NCCN guidelines recommend nivolumab + ipilimumab, nivolumab + relatlimab, and anti-PD-1 monotherapy as category 1 preferred first-line (1L) treatments (txs) for advanced melanoma. These immunotherapies (IOs) however differ in administration, efficacy, and safety. Given these differences, this study examines oncologists (oncs) and patients (pts) preferences when choosing 1L tx. **Methods:** Pts with self-reported unresectable or metastatic melanoma and oncs completed an online cross-sectional survey. A discrete choice experiment assessed preferences for three efficacy attributes, three safety attributes, and dosing schedule. Attributes (shown in table) were identified via literature and qualitative research. Each attribute had two or three levels based on clinical trial data of recommended IOs. Participants completed 12 tasks; each task showed two tx options with varying levels for each attribute. Hierarchical Bayesian modeling was used to estimate preference weights for each level and relative importance estimates, based on the range between levels, were computed. **Results:** 75 oncs (male 76%; mean age 46 years; community-based 51%) and 62 pts (male 68%; mean age 43 years) were analyzed (pt recruitment ongoing; target n = 75). For both oncs and pts, improvements in safety attributes was more important than improvements in efficacy attributes (pts: 50.3 vs. 33.9; oncs: 48.6 vs. 40.9). For safety, a decrease in risk of discontinuation due to treatment-related adverse events (TRAEs) was most important in oncs (24.7); while for pts, lower risk of grade 3/4 TRAEs was most important (22.6). For efficacy, an increase in overall survival (OS) was most influential for oncs (21.0); pts had similar estimates within efficacy. Dosing schedule was third most important for pts (15.8), while it was among the least important for oncs. **Conclusions:** Oncs and pts prioritize minimizing the risk of serious AEs when efficacy differences are minimal in 1L advanced melanoma tx choice. These findings highlight that oncs and pts value an IO with an efficacy benefit while ensuring a favorable risk-benefit profile. This information can inform tx counseling and selection discussions among oncs and pts. Research Sponsor: Bristol Myers Squibb.

Relative importance (mean ± SE) of IO attributes influencing oncs and Pts 1L Tx choice.

Attributes (Level Range)	Oncs (N = 75) Mean ± SE	Pts (N = 62) Mean ± SE
Safety (net)	**48.6 ± 1.7**	**50.3 ± 1.6**
Discontinuation due to TRAEs (7-40%)	24.7 ± 1.4	17.6 ± 1.3
Grade 3 / 4 TRAEs (10-60%)	19.8 ± 1.0	22.6 ± 1.4
Endocrine AEs (18-35%)	4.2 ± 0.4	10.1 ± 1.0
Efficacy (net)	**40.9 ± 1.8**	**33.9 ± 1.6**
24-Month OS (55-65%)	21.0 ± 1.7	11.2 ± 1.0
24-Month PFS (28-41%)	12.5 ± 1.0	9.7 ± 1.0
24-Month ORR (36-50%)	7.5 ± 0.6	13.1 ± 1.0
Dosing schedule (2 IVs every 3 wks for 4 doses then IV every 4 wks; IV every 6 wks; IV every 4 wks)	**10.5 ± 0.7**	**15.8 ± 1.3**

PFS = Progression free survival; ORR = Objective response rate; IV = intravenous; wks = weeks; SE = standard error.

9540 Poster Session

Advanced stage melanoma during pregnancy: Real-world management.

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Background: Treatment (tx) of advanced melanoma during pregnancy represents a major challenge. While management of early-stage melanoma is similar to non-pregnant patients (pts), very little data is available on outcome or tx guidelines for pregnant pts with advanced stage. Therefore, we collected real world management data, to ultimately develop management guidelines for these pts. **Methods:** This retrospective, international, multicenter database, included pts who either were diagnosed with advanced melanoma (newly diagnosed or recurrent) during pregnancy (group 1) or conceived while on systemic tx for melanoma (group 2) between 01/2011–06/2023. Patient, primary tumor and advanced melanoma characteristics, intervention/tx during pregnancy, and outcomes of mother and fetus were collected using a standardized, de-identified form. **Results:** 68 pts from 7 countries were included, with a total of 72 pregnancies: 60 pregnancies in group 1 and 12 in group 2, including 5 twin pregnancies. Median age at time of pregnancy was 32 (19-42). In group 1, advanced melanoma diagnosis occurred during the 1st trimester in 38%, followed by 3rd (32%), 2nd (22%) and unknown (8%) trimester. 2% had stage II melanoma, 48% stage III, and 50% stage IV. 76% were cutaneous melanoma, 7% mucosal, and 17% other subtypes. *BRAF* mutations were seen in 70%. Pregnancy was terminated in 15% of cases, and miscarriage occurred in 1 case. Of the 50 live births, 68% were induced and 56% were preterm (38% vaginal, 54% C-section). Median gestational age (MGA) was 34 wks (27-40). Systemic tx was initiated during pregnancy in 8 pts (targeted therapy [TT, 63%], immunotherapy [IT, 37%]). 90% switched or initiated new systemic tx after pregnancy (median time to start of therapy: 28 days; IT 65%, TT 27%, chemo 8%). 5-year overall survival (OS) was 49% (95%CI 34-69), with a median follow-up (MFU) of 26m. In group 2, 82% had cutaneous melanoma and 18% an unknown primary. 91% had a *BRAF* mutation. 42% of pts received systemic tx for stage III melanoma and 58% for stage IV (IT 75%, TT 25%). 33% of pregnancies were terminated, 8% ended in miscarriage. Of the 8 live births, 43% were preterm, 29% were induced (43% vaginal, 29% C-section). MGA was 35 wks (32-39). Half the pts initiated new or continued tx after pregnancy (IT 50%, TT 50%). 5-year OS was 78% (95%CI 55-100), with MFU of 48m. Of the 57 live births, 1 child born at 26w died after 3 days. No children developed melanoma, despite 5 placentas with melanoma involvement. 4 unexposed children had congenital deficits: prematurity-related (n=3) and congenital hypothyroidism (n=1). 1 child with 3rd trimester Vemurafenib exposure had heart malformations, and 2 experienced toxicity after *in utero*ITexposure. **Conclusions:** This is the largest contemporary dataset of pts diagnosed with advanced melanoma during pregnancy and pts who became pregnant on systemic melanoma therapy, and provides a basis for developing clinical guidelines for this challenging population. Research Sponsor: None.

9541 Poster Session

Circulating tumor DNA analysis in patients with BRAF-mutated metastatic cutaneous melanoma treated with BRAF and MEK inhibitors: Analysis of the OPTIMEL study.

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Background: BRAF and MEK kinase inhibitors (KI) are indicated in combination for the treatment of adult patients with unresectable or metastatic melanoma (MM) harboring a BRAF V600 mutation. However, approximately half of the patients develop resistance to the treatment within a year. Circulating tumor DNA (ctDNA) has demonstrated its prognostic value for MM patients receiving specific treatment, offering potential assistance in patient follow-up. We present here the results of the prospective interventional study OPTIMEL (NCT03416933) that was conducted to investigate the relevance of ctDNA in predicting outcomes for MM patients undergoing BRAF and MEK inhibitors treatment. **Methods:** Thirty-five patients with histologically proven advanced cutaneous MM harboring *BRAF* mutations, either in a metastatic stage or cases ineligible for surgical intervention were enrolled in the study. All participants underwent treatment with BRAF and MEK inhibitors. Blood samples were systematically obtained on days 0, 15, 30, 90, 180, 270, and 365, or at the occurrence of disease progression. The assessment of mutations in the *BRAF* and *NRAS* genes in all plasma samples was conducted using the Idylla system (Biocartis, Mechelen, Belgium). **Results:** Out of the 35 patients initially enrolled in the study, 4 were excluded for not meeting the inclusion criteria, leaving 31 patients for the final analysis. At baseline, *BRAF* mutation was identified in 18 patients (58%), while it was not detected in 13 patients (42%). The presence of *BRAF* mutation at baseline was associated with a significantly lower progression-free survival (PFS) (HR = 3.42; CI95% [1.19;9.82]; p = 0.022). During the follow-up, *BRAF* mutation was detected in the plasma of 19 out of 31 patients. A *BRAF* variant allele frequency (vaf) below 2.3% was strongly linked to an objective response to treatment ($p<0.001$). The absence of *BRAF* variant detection during follow-up was significantly associated with better outcome (PFS 4.01 vs 12.0 months, HR = 28.5; CI95% [7.75;105.0]; $p < 0.001$). Moreover, PFS significantly deteriorated when *BRAF* vaf exceeded 4.5% (3.15 vs 12.0 months, HR = 112; CI95% [13.8;913.0]; $p < 0.001$). Lastly, the identification of *NRAS* mutation in plasma during follow-up was linked to treatment resistance and a worsened PFS (4.84 vs 10.9 months, HR = 11.6; CI95% [2.76;48.5]; $p<0.001$). **Conclusions:** This report presents the initial analysis of the OPTIMEL study. The variant allele frequency of *BRAF* mutations in circulating tumor DNA is indicative of the objective response to BRAF and MEK inhibitors, as well as PFS. These findings could potentially influence our approach to managing patients with MM harboring a *BRAF* mutation. Clinical trial information: NCT03416933. Research Sponsor: Institut de Cancérologie de Lorraine; Novartis; Biocartis.

9542 Poster Session

Retro TIMing: A multicentric retrospective analysis of immunotherapy timing in metastatic melanoma.

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Background: Immune checkpoint inhibitors (ICI) targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are now the standard of care in the treatment of metastatic melanoma (mM). The interplay between cancer cells and tumor microenvironment cells (e.g. immune cells) impacts cancer cell survival, local invasion, and metastatic dissemination. Chrono-immunotherapy is an emerging field as circadian oscillations are observed in the immune landscape (e.g immune cell numbers) as well as in the expression of immunotherapy targets (e.g. PD-1). Recently, a growing body of evidence suggests the outcome can be influenced by the time of the day when immunotherapy is administered (morning *versus* in the afternoon). This work aims to evaluate the impact of immunotherapy with ICIs administration timing on the overall survival (OS) and progression-free survival (PFS) of patients with mM. **Methods:** Multicentric, retrospective cohort study of mM patients under immunotherapy (ipilimumab/nivolumab, nivolumab, or pembrolizumab) with PS 0-1, between July 2016 and June 2023. Clinical, demographic characteristics, and time of treatment administration were obtained from medical records. Patients were distributed in two groups: those who received less than 75% of infusions after 2pm (morning group), and those who received at least 75% of infusions after 2pm (afternoon group). OS and PFS were calculated with Kaplan-Meier method and tested using a Cox regression model, with a 95% confidence interval. **Results:** We identified 168 patients from the 7 Oncology Centers included. The majority were men (n=100, 59.5%), with a median age of 69 years old, and 22% of the patients (n=37) were included in the afternoon group. No significant demographic or tumor burden differences were found between the morning and afternoon groups. The median follow-up time was 29 months, the estimated median PFS was 11.8 months (CI 95%, 8.0 - 14.6) and median OS was 31.4 months (CI 95%, 20.6 - NR). Patients in the afternoon group presented with shorter OS compared with those in the morning group (14.4 vs 37.6 months; HR 1.94 [CI 95% 1.16 to 3.23]; p 0,014). No statistically significant differences were observed in PFS. Subgroup analysis showed an increased detriment of performing ICIs infusions in the afternoon in women (OS 8.7 (4.2, 21.2) *versus* 30.9 months (18.9, NR), p=0.002; afternoon *versus* morning) and those older than 65 years old (OS 14.2 months (4.7, 31.4) *versus* 24.2 months (18.3, NR), p=0.002); afternoon *versus* morning). **Conclusions:** This work provides valuable insights into the potential role of the circadian timing of immunotherapy treatments for mM, suggesting patients may benefit from having ICIs infusion in the morning. Prospective randomized studies with a translational approach are needed to validate and fully understand the underlying mechanisms at play in circadian timing efficacy. Research Sponsor: None.

9543 Poster Session

High dose bolus (HDB) interleukin-2 (IL2) and concurrent low dose ipilimumab followed sequentially by nivolumab in patients with advanced melanoma after failure of anti-PD1-based immunotherapy and BRAF-MEK inhibition.

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Background: Options are limited for patients with advanced metastatic melanoma who have disease progression following anti-PD1-based immunotherapy and BRAF-MEK inhibition (if BRAF V600 mutant). Evidence supports synergism between IL2 and CTLA4 blockade in enhancing the immunogenicity of the tumor microenvironment and therapeutic susceptibility to PD1 blockade. **Methods:** We conducted a phase II study of HDB IL2 in combination with LD ipilimumab followed sequentially by nivolumab in patients with advanced inoperable stage III or stage IV melanoma with progression after anti-PD1-based immunotherapy and BRAF-MEK inhibitors. Treatment consisted of up to 3 courses (One cycle is 21 days and one course is 4 cycles). HDB IL2 and concurrent ipilimumab 1 mg/kg were given during week 1 of the initial 2 cycles of each course. Nivolumab was given during week one of the 3rd cycle of each course. Patients without evidence of disease progression (RECIST v.1.1) or limiting toxicities (CTCAE v.5) were offered additional courses of treatment. A Simon two-stage minimax design (Simon, 1989) was followed. We report the outcomes for Stage I. **Results:** 12 pts (5 female, 7 male) with metastatic melanoma (2M1a, 1M1b, 6M1c, 3M1d) were treated. Median age 53 years (33 – 69), 11 cutaneous (including 1 acral) and 1 mucosal primary. Tumor mutation status: 4BRAF (V600E), 2NRAS (p.Q61K), 1NF1. The median number of prior regimens for metastatic melanoma was 3 (range 1 - 5). Eight patients previously received ipilimumab as monotherapy or in combination with anti-PD1. On study, the median number of doses of IL2 was 9 during cycle 1 and 7 during cycle 2. A median of 2 doses of ipilimumab and 1 dose of nivolumab were given as part of the combination regimen. Among the 11 evaluable patients (completed 1 course of systemic therapy), the response rate was 2/11 (18.2 %; 95% CI: 2.3% – 51.8%); 1CR, 1 PR, 5 SD, 4 PD and 1 NE as best response. After a median follow up of 39 months, both responses are ongoing (at 10+ and 37+ months), median progression free survival (PFS) was 3 months and median overall survival (OS) was 18.8 months. One-year PFS and OS were 17% (95% CI: 4.7% - 59%) and 83% (95% CI: 65% - 100%), respectively. The adverse event profile was consistent with the expected toxicity profile for each agent with no increase in frequency with the combination. **Conclusions:** Our combination regimen was relatively safe and well tolerated and demonstrated promising efficacy in a heavily pretreated patient population passing the prespecified efficacy criteria for Simon Stage I. The study has moved into Stage II testing. Clinical trial information: NCT04562129. Research Sponsor: Iovance.

9545 Poster Session

Overall survival and efficacy subgroup analysis 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) has showed an encouraging efficacy (confirmed ORR:34.8%, mPFS:4.2 months) with a manageable safety profile in phase II pivotal registrational study, which was published in ASCO 2023 annal meeting (NO.:9510). Here, we report the updated efficacy results. **Methods:** This is a multicenter, single-arm, phase II, pivotal registrational study. Patients (pts) with NRAS-mutant unresectable stage III or IV melanoma were enrolled and received tunlametinib 12 mg orally twice daily. The primary endpoint was confirmed objective response rate (ORR) per Response Evaluation Criteria In Solid Tumors, version 1.1 assessed by independent radiology review committee (IRRC). **Results:** A total of 100 pts were enrolled and 95 pts were included in the full analysis set (FAS) for efficacy analysis. At cut-off date (October 31, 2023), median follow-up was 24.4 months (95% CI: 21.9, 27.9). The confirmed ORR was 35.8% (95%CI: 26.3%, 46.3%). Median progression-free survival (mPFS) was 4.2 months (95%CI: 3.5, 5.6). The median overall survival (mOS) was immature during last year's ASCO annual meeting, and the present mOS was 13.7 months (95% CI of 10.3–18.0). The IRRC-assessed ORRs by melanoma subtype were 42.9% (95% CI of 29.7–56.8) in acral melanoma, 25.0% (95% CI of 7.3–52.4) in mucosal melanoma. ORRs by *NRAS*mutation site were 41.3% (95% CI of 30.1–53.3), 13.3% (95% CI of 1.7–40.5) and 20.0% (95% CI of 0.5–71.6) for Q61, G12, and G13, respectively. ORR in patients who had been treated with immunotherapy was 40.6% (95% CI of 28.5–53.6), while in those without immunotherapy, ORR was 25.8% (95% CI of 11.9–44.6). The difference in PFS was not statistically significant across subgroups, regardless of melanoma type, *NRAS* mutation site, line of previous treatment, type of previous treatment and previous treatment with immunotherapy. The safety profile is similar with last year's ASCO annual meeting. The most frequent treatment related adverse events (TRAEs) were increased blood creatine phosphokinase (CK), diarrhea, facial oedema, peripheral oedema, and increased aspartate aminotransferase. No treatment-related death was reported. **Conclusions:** Tunlametinib demonstrated an encouraging treatment response rate in patients with advanced NRAS-mutant melanoma with a manageable safety profile. These results suggest that tunlametinib could be a promising treatment option for NRAS-mutant melanoma, even for those who had previously received immunotherapy. Clinical trial information: NCT05217303. Research Sponsor: Shanghai KeChow Pharma.

Real-world outcomes of combined lenvatinib and anti-PD-1 in advanced melanoma: Lenvamel, a multicenter retrospective study of the French Group of Skin Cancers.

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Background: Treatment options for patients (pts) with advanced melanoma who experience resistance to immunotherapy (ICI) +- targeted therapy are lacking. Studies suggest the anti-tumour activity of combined pembrolizumab and lenvatinib in pts progressing on ICI. We report the clinical outcomes of combined lenvatinib and anti-PD-1 in this population. **Methods:** This French multicenter real-world study was conducted from 09/2020 to 07/2023. The primary endpoint was objective response rate (ORR) according to the RECIST criteria (v.1.1). Secondary endpoints were treatment-related adverse events (TRAEs), progression-free survival (PFS), overall survival (OS) and duration of response (DOR). **Results:** Of the 67 pts included (median age, 69 years; median follow-up, 5.0 months), 85% had stage IV M1c or M1d disease. Baseline characteristics are presented (Table). Overall ORR was 28.4% (95%CI, 18–41%), including 3 complete (4.5%) and 16 partial (23.9%) responses. ORR was 71.4% (95%CI, 29–96%) for mucosal melanoma, 32,8% (95%CI, 21–46%) for pts pre-treated with anti-PD-1 + anti-CTLA-4, and 31,5% (95%CI, 20–46%) for *BRAF* wild-type melanoma. Median DOR was 3.1 (IQR, 1.3–4.3) months. Median PFS and OS were 3.1 (95% CI, 2.5–3.7) and 9.8 (95% CI, 5.6–13.9) months respectively. Grade 3–4 TRAEs occurred in 16 pts (24%, no grade 5); common TRAEs were fatigue (43.3%), nausea/vomiting (26.8%), diarrhea (20.9%), and hypertension (20.9%). **Conclusions:** Our study demonstrates an interesting response rate and acceptable safety profile of this combination, with manageable toxicities, in an immuno-refractory population with poor prognostic factors. Pts pre-treated with anti-PD-1+ anti-CTLA-4, and those with *BRAF* wild-type melanoma seemed to benefit more from this strategy. Our study also provides promising data (considering the small sample) for pts with mucosal melanoma. Our data support this treatment option for refractory melanoma, though not yet approved by the health authorities, and highlight the need for new strategies. Research Sponsor: None.

Baseline Characteristics	All Patients (N=67)
Age, years, median (range)	69 (27-88)
Sex, N (%)	
Men	33 (49)
Primary melanoma, N (%)	
Cutaneous	54 (81)
Mucosal	7 (10)
Unknown	6 (9)
AJCC 8th edition, N (%)	
III	2 (3)
IV	65 (97)
- M1a	1 (2)
- M1b	7 (10)
- M1c	28 (42)
- M1d	29 (43)
Active brain metastasis, N (%)	20 (30)
- Concomitant brain stereotactic radiosurgery	14 (70)
Number of disease sites, N (%)	
>3	42 (63)
ECOG, N (%)	
0	23 (34)
1	35 (52)
≥2	9 (14)
Mutation Status, N (%)	
BRAF V600	13 (19)
LDH, N (%)	
Normal	33 (49)
N > ULN and < 2ULN	20 (30)
N ≥ 2ULN	6 (9)
Unknown	8 (12)
Number of prior lines of therapy, N (%)	
1	19 (28)
2	18 (27)
≥3	30 (45)
Prior line with anti-PD-1 + anti-CTLA-4, N (%)	58 (87)
Resistance to anti-PD-1, N (%)	
- Primary resistance in the adjuvant setting	8 (12)
- Primary resistance in the metastatic setting	29 (43)
- Secondary resistance in the metastatic setting	30 (45)

9547 Poster Session

Camrelizumab plus apatinib and temozolomide as first-line therapy for advanced acral melanoma: 2-year survival results from CAP 03.

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Background: Acral melanoma is the predominant subtype in Asia, which presents with aggressive biological behavior. First-line immunotherapy yields modest efficacy in advanced acral melanoma, suggesting the need of combination therapy. Our CAP 03 study investigated the combination of anti-PD-1 antibody plus antiangiogenic agent and chemotherapy for the first-line treatment of advanced acral melanoma, and the primary analysis has been published on JAMA Oncology in June 2023 (objective response rate [ORR], 64%; median progression-free survival [PFS], 18.4 months). Here we updated the efficacy results with a median follow-up of 30.3 months (95% CI, 28.9-32.5; reverse Kaplan-Meier method) at data cutoff date on January 8, 2024. **Methods:** In this single-center phase 2 trial (NCT04397770), patients with pathologically confirmed unresectable stage III or IV acral melanoma and without prior systemic therapy for advanced disease were recruited. Patients received first-line intravenous camrelizumab (200 mg once every 2 weeks) plus oral apatinib (250 mg once a day) and intravenous temozolomide (200 mg/m^2 once a day on days 1-5 every 4 weeks) until disease progression or intolerable toxicity. The primary endpoint was ORR per Response Evaluation Criteria In Solid Tumors, version 1.1. Imaging assessment was performed after 4 weeks, then every 8 weeks until one year, and every 3 months thereafter. Overall survival (OS) was followed every 3 months. **Results:** Between May 2020 and August 2021, a total of 50 patients were enrolled. The confirmed ORR was 66.0% (33 of 50; 95% CI, 51.2%-78.8%). The median PFS was 21.2 months (95% CI, 10.1-27.1). The median OS was not reached, and the 1-year and 2-year OS rates were 88.0% (95% CI, 75.2%-94.4%) and 64.8% (95% CI, 49.5%-76.5%), respectively. Further analyses indicated comparable PFS benefit in subgroups by age (<65 years vs ≥65 years), sex (male vs female), Eastern Cooperative Oncology Group performance status (0 vs 1), *NRAS* status (variant vs wild-type), stage, lactic dehydrogenase (LDH) level, and PD-L1 combined positive score (<5 vs ≥5). Regarding OS, similar trends were observed in these subgroups, except that patients with normal LDH had better median OS than those with elevated LDH (not reached vs 22.6 months, log-rank nominal P=0.033). **Conclusions:** This first-line triplet combination shows encouraging survival benefits in patients with advanced acral melanoma, regardless of *NRAS* status or PD-L1 expression level. Follow-up is still ongoing to obtain mature OS data. Clinical trial information: NCT04397770. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

9548 Poster Session

Using serial 18F-FDG PET/CT PERCIST response to predict responses to immune check point inhibitors in patients with advanced cutaneous squamous cell carcinoma.

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Background: The role of serial 18F-FDG-PET/CT imaging in predicting long term efficacy of PD-1 targeted immune checkpoint inhibitor (ICI) in advanced cutaneous squamous cell carcinoma (cSCC) is unknown. This study aims to correlate PET PERCIST response with time to progressive disease. **Methods:** This was a single-centre retrospective study of patients treated with ICI for advanced cSCC who had baseline and serial FDG-PET/CT within 4-months of commencement of ICI. PERCST 1.0 was calculated by two radiologists independently and classified into complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD). The primary endpoint was time to progression from commencement of ICI. Progression was determined by a multidisciplinary team combining clinical and radiological assessments. **Results:** Of the 242 patients treated with ICI for advanced cSCC during 2018-2023, 83 (34%) patients had a serial FDG PET. Of these, 53 patients met the inclusion criteria of ≤4-months from ICI to second PET. CMR (54.7%), PMR (15.1%), SMD (11.3%) and PMD (18.9%) were seen as initial responses by PERCST 1.0. With a median follow-up of 8-months (1-55), progressive disease as determined by the multidisciplinary team was observed in 11 patients (21%). For these 11 patients, the 4-month PERCST 1.0 response was measured as CMR (n=1), PMR (N=1), SMD (N=2) and PMD (N=7). The median TTP was significantly higher in CMR/ PMR vs SMD/PMD (55 vs 4-Months, $P<0.001$). At data cut off, 94.6% (N=35) of patients with a 4-month PET PERCST 1.0 CMR/ PMR assessment did not progress clinically. Clinical response was maintained at a minimum of 12-months in 94.7% (n=18) of those responding. **Conclusions:** Rate of CMR and PMR in advanced cSCC is high with ICI. Early PET CMR/ PMR appears to predict long term durable responses. Incorporation of PET/CT into the assessment of response in cSCC may help guide treatment decisions by early identification of those patients not responding to ICI. Research Sponsor: None.

Atezolizumab (A), cobimetinib (C), and vemurafenib (V) in patients (pts) with *BRAF*^{V600} mutation–positive melanoma with central nervous system (CNS) metastases (mets): Final results and exploratory biomarker analysis from the phase 2 TRICOTEL study.

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Background: Primary analysis results from the phase 2 TRICOTEL study showed intracranial activity with the triplet combination of A + C + V in pts with *BRAF*^{V600}-mutated melanoma with CNS mets (1). Here, we report final analysis results and exploratory biomarker analyses for pts with *BRAF*^{V600}-mutated melanoma in the triplet combination cohort from TRICOTEL. **Methods:** Eligible pts were aged ≥18 y and had melanoma, MRI-confirmed CNS mets ≥5 mm in ≥1 dimension, and no prior systemic treatment for metastatic disease. Pts received A (840 mg on days 1 and 15 of each 28-d cycle) + C (60 mg once daily for 21 d on, 7 d off) + V (720 mg twice daily) except in cycle 1, during which A was withheld. Tumor tissue and circulating tumor DNA (ctDNA) samples collected at baseline (cycle 1, day 1) and ctDNA at the time of progressive disease (PD) were profiled for mutations using next-generation sequencing. Tumor tissue was profiled using a pipeline programmed for MelArray, and ctDNA was measured based on the tissue genetic profile. **Results:** A total of65 pts were enrolled in the triplet combination cohort. At final analysis, median follow-up was 12.4 mo. Per independent review committee (IRC) assessment, intracranial ORR (confirmed by assessments ≥4 wk apart) was 38% (95% CI, 27–51) and median intracranial PFS was 5.1 mo (95% CI, 3.7–6.9) (Table). Median OS was 13.4 mo (95% CI, 10.7–16.9). No new safety signals were observed since primary analysis. Mutations were detected in baseline ctDNA samples of 60 pts (5 pts not reported) and showed high prevalence of *NF1*, *NRAS*, and *GNAI2* mutations; relative to tumor tissue, 11 additional *BRAF* mutations were detected in ctDNA at baseline. Acquired mutations in *AKT1* were detected in ctDNA at PD. Median OS shortened in pts with >2 versus ≤2 mutated MAPK pathway genes in ctDNA at baseline (9.1 vs 14.5 mo; hazard ratio, 2.0 [95% CI, 1.0–3.7]; $p<0.05$). In tumor tissue, baseline mutations in *PIK3C2A* and *PLEKHG4* were enriched in nonresponders, while *RAD51B* mutations were enriched in responders. **Conclusions:** Combination A + C + V had clinical intracranial activity in pts with *BRAF*^{V600}-mutated melanoma with CNS mets. Exploratory biomarker analyses in this small cohort demonstrate the presence of ctDNA in pts with melanoma and CNS mets and provide insight into mutations associated with response and resistance to the triplet combination. 1. Dummer R et al, *Lancet Oncol* 2023. Clinical trial information: NCT03625141. Research Sponsor: F. Hoffmann-La Roche Ltd.

Outcomes at final analysis (N=65).

	Intracranial (IRC)	Intracranial (investigator)	Extracranial (investigator)	Overall (investigator)
ORR, % (95% CI)	38 (27–51)	49 (37–62)	57 (44–69)	52 (40–65)
Median duration of response, mo (95% CI)	6.2 (4.8–9.4)	6.7 (5.6–9.5)	11.6 (9.2–13.0)	7.4 (5.5–9.5)
Median PFS, mo (95% CI)	5.1 (3.7–6.9)	5.8 (5.4–7.4)	10.7 (7.9–13.7)	5.5 (5.1–7.4)

9551 Poster Session

Development of a novel granulocyte scoring system for use as a predictive/prognostic biomarker in patients with advanced melanoma undergoing treatment with combination immunotherapy.

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Background: Despite the implementation of immune checkpoint inhibition (ICI) for patients with metastatic melanoma, there remains an unmet clinical need for predictive/prognostic biomarkers to determine, from outset, which patients will derive benefit. Recent literature has suggested a significant role for granulocyte subsets in the development of resistance to systemic therapies, with an associated role in adaptive immunity. **Methods:** We sought to establish a novel immunological scoring system to use as a predictive/prognostic biomarker in patients with advanced melanoma being treated with ICI. In this retrospective, single centre study evaluating patients with advanced melanoma treated with combination ipilimumab and nivolumab, progression free survival (PFS) and overall survival (OS) were compared between groups defined by neutrophil, lymphocyte, eosinophil, monocyte and basophil counts. Data from 226 patients was collected at baseline, week 3, week 6, first response scan and at progression. Baseline and week 3 data was the focus of this primary analysis. Kaplan-Meier estimation and Cox regression analysis were performed. **Results:** Univariate analysis demonstrated that absolute neutrophil, eosinophil and basophil count strongly associates with PFS and OS outcomes at week 3. Combination of these counts into a novel neutrophil to eosinophil + basophil ratio (NEBR, (N/(E+B)) was assessed as a scoring system. High NEBR was associated with poorer PFS and OS at baseline and week 3 with consistently superior predictive/prognostic value than the well-established neutrophil to lymphocyte ratio (NLR). After accounting for covariates including concurrent steroids, infection and LDH, high NEBR remained significantly associated with worse PFS at baseline and poorer PFS and OS at week 3. **Conclusions:** Our findings highlight NEBR as a novel immunotherapeutic predictive/prognostic biomarker with potential clinical utility that warrants further investigation in patients with advanced melanoma and across other tumour groups. Further validation will be required through independent external datasets. Research Sponsor: None.

	PFS Baseline	PFS Week 3	OS Baseline	OS Week 3
HR Absolute neutrophils (95% CI)	1.5 (1.1-2) p=0.01	2.2 (1.6-3) p=<0.01	1.7 (1.2-2.5) p=<0.01	2.1 (1.5-3) p=<0.01
HR Absolute eosinophils	0.76 (0.63-0.92) p=0.04	0.69 (0.59-0.81) p=<0.01	0.77 (0.63-0.94) p=0.012	0.69 (0.59-0.81) p=<0.01
HR Absolute basophils	0.81 (0.61-1.1) p=0.16	0.65 (0.49-0.85) p=<0.01	0.89 (0.65-1.2) p=0.46	0.59 (0.44-0.8) p=<0.01
LDH	2.04 (1.47-2.84) p=<0.01	1.39 (1.01-1.93) p=0.05	2.5 (1.75-3.58) p=<0.01	1.36 (0.96-1.92) p=0.08
NLR	1.27 (0.92-1.75) p=0.15	1.58 (1.13-2.21) p=<0.01	1.35 (0.96-1.90) p=0.09	1.56 (1.08-2.23) p=0.02
NEBR	1.68 (1.21-2.33) p=<0.01	2.00 (1.42-2.82) p=<0.01	1.65 (1.16-2.34) p=<0.01	2.35 (1.61-3.42) p=<0.01

9552 Poster Session

ADU-1604, a novel CTLA-4 blocking antibody, to modulate pharmacodynamic markers in patients with PD1 relapse/refractory melanoma.

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Background: Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a negative regulator of T-cell responses, also known as an immune checkpoint. The clinical relevance of CTLA-4 blockade was demonstrated by the approval of ipilimumab for the treatment of melanoma, both in the adjuvant as well as metastatic settings. ADU-1604 is a humanized hIgG1 CTLA-4 antagonist antibody. ADU-1604 binds a unique epitope on CTLA-4 demonstrating, in contrast to ipilimumab full blockade of both CD80 and CD86 interactions. In vitro and in vivo ADU-1604 demonstrates at least as potent efficacy as compared to ipilimumab, was well tolerated in non-human primates and demonstrated enhanced immunogenicity against hepatitis B vaccine in non-human primates. **Methods:** This is a phase 1, first-in-human (FIH), two-part, open-label clinical trial of intravenous (IV) administration of ADU-1604 given as monotherapy in subjects with advanced-stage, relapsed/refractory melanoma who relapsed or were refractory to a prior anti-PD-1/PD-L1 therapy. Main endpoints are safety of ADU-1604 monotherapy, pharmacokinetics, pharmacodynamics (upregulation of ICOS and Ki-67 on circulation CD4+ T cells and ALC, CD4+ and CD8+ T cells) as well as preliminary clinical efficacy. 20 subjects received escalating doses of ADU-1604 IV (25, 75, 225, 450 mg flat dose) Q3W. In the dose expansion part up to 20 additional patients will be treated with 225 mg dose to confirm recommended Phase 2 dose (RP2D). Safety and preliminary efficacy of ADU-1604 monotherapy in PD1 relapsed/refractory melanoma patients will be evaluated. The study was initiated in June 2022. **Results:** ADU-1604 was demonstrated to have a typical pharmacokinetic behavior for a human IgG1 antibody and similar exposure was observed as described for ipilimumab. Administration of ADU-1604 in cycle 1 and 2 showed a dose-dependent modulation of ICOS and Ki-67 on circulating CD4+ T cells. Similarly, in cycles 3 and 4 a dose-dependent increase of ALC and CD4+ and CD8+ T cells was detected. Notably, no DLTs across the 25, 75, 225 and 450 mg dose level have occurred. Of the patients treated at 225 and 450 mg dose levels (N=6 at 225 mg and N=6 at 450 mg), two Grade 2 severe adverse events (both immune-related enterocolitis) and two Grade 3 AESIs (ALT elevation and immune-related gastritis) suggesting that ADU-1604 has a relatively mild safety profile. Two patients at 225 mg and one patient at 450 mg demonstrated clinical efficacy. **Conclusions:** ADU-1604 Phase 1 dose-escalation data indicates clinical activity in line with what has been observed with other CTLA-4 blocking antibodies. Importantly, no DLTs and very limited safety signals were reported during the study. Dose expansion at 225 mg dose is ongoing in subjects with advanced-stage, relapsed/refractory melanoma who relapsed or were refractory to a prior anti-PD-1/PD-L1 therapy. Clinical trial information: 2021-002623-38. Research Sponsor: Sairopa b.v.

9553 Poster Session

Phase II trial of weekly or bi-weekly tocilizumab with ipilimumab and nivolumab in advanced melanoma: Clinical outcomes and biomarker analysis.

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Background: Combination immune-checkpoint inhibitors (ICIs) improved outcomes in a plethora of cancer subtypes. However, up to 60% of patients (pts) receiving ipilimumab (ipi) plus nivolumab (nivo) experience grade 3/4 (G 3/4) immune-related adverse events (irAEs), often leading to treatment discontinuation. We evaluated two therapeutic strategies targeting interleukin-6 receptor (IL-6R) to reduce irAEs while enhancing ICls efficacy. **Methods:** Phase Il trial (NCT04940299) investigating safety/efficacy of frontline tocilizumab (toci; IL-6R inhibitor) combined with ipi 3mg/kg + nivo 1mg/kg Q3 weeks (wks) for 12 wks in advanced melanoma. Initially, toci was given as 162 mg subcutaneously (SQ) bi-weekly for 6 doses (regular dosing regimen; RD). Then, we escalated to a dose dense (DD) regimen (162 mg SQ weekly for 6 wks then bi-weekly for 6 wks; 9 doses total). Primary objective was rate of G 3/4 irAEs. Secondary objectives were objective response rates (ORR) and disease control rate (DCR) per RECIST 1.1. Exploratory objectives involved immune analysis (gene expression, CyTOF, cytokine analysis) on longitudinal blood and tissue samples to identify drivers of auto- vs antitumor immunity. **Results:** As of Feb 2024, 35 pts were enrolled (25 pts to RD regimen; 10 pts to DD regimen). In RD group, median follow-up is 18 months (6 - 25 months). By 12 wks, 44% of pts developed G 3/4 irAEs including colitis (20%), hepatitis (16%), pancreatitis (12%), type I diabetes and serum sickness (4% each) and 20% of pts required hospitalization due to irAEs. Median time to G 3/4 irAEs onset was 7.4 wks. 16% of pts discontinued ICIs due to irAEs. ORR was 56% at 12 wks including 40% in pts with high LDH and DCR was 80%. Gene expression analysis showed a trend towards higher expression of IL-17 pathway genes in pts who developed G 3/4 irAEs, suggesting IL-6/Th17 pathway was not sufficiently inhibited. Thus, we enrolled 10 pts into the DD regimen aiming to achieve better inhibition of the IL-6/Th17 pathway. In DD group, median follow-up is 7 months (3 - 13 months). By 12 wks, 40% of pts developed G 3/4 irAEs, including colitis (10%), hepatitis (20%), and uveitis (10%) and 30% of pts required hospitalization due to irAEs. Median time to G 3/4 irAEs onset was 4.9 wks. 30% of pts discontinued ICIs due to irAEs. ORR was 70% at 12 wks including 75% in pts with high LDH and DCR was 80%. **Conclusions:** To our knowledge, this is the first study to investigate toci in combination with high dose ipi3/nivo1. Although our cohort is small, preliminary data suggests IL-6R blockade using the DD regimen could decrease the rate of G 3/4 irAEs while maintaining antitumor responses of ipi3/nivo1. A randomized phase ll trial investigating this strategy is underway. Ongoing immune analysis comparing treatment regimens aims to identify distinct pathways involved in auto- vs antitumor immunity and IL-6/Th17 independent pathways of toxicity. Clinical trial information: NCT04940299. Research Sponsor: NIH K01 award; MD Anderson Cancer Center Prioritizing Research Innovation and Mentoring Excellence Award; MD Anderson Melanoma SPORE Career Enhancement Program Award; ASCO Conquer Cancer Foundation Young Investigator Award; 2019YIA-2914078105; MD Anderson Immunotherapy Platform.

Pembrolizumab (pembro) for locally advanced (LA) or recurrent/metastatic (R/M) cutaneous squamous cell carcinoma (cSCC): Long-term results of the phase 2 KEYNOTE-629 study.

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Background: Pembro monotherapy is approved in certain countries, including the US, for treatment of LA or R/M cSCC based on results from the open-label phase 2 KEYNOTE-629 trial (NCT03284424). Promising antitumor activity was demonstrated with pembro in both the LA and R/M cohorts. ORR (95% CI) was 50.0% (36.1-63.9; 16.7% CRs) in the LA cohort and 35.2% (26.2-45.2; 10.5% CRs) in the R/M cohort. We present data from KEYNOTE-629 with an additional follow-up of 38 mo for LA and R/M cohorts. **Methods:** Adults with histologically confirmed LA or R/M cSCC, measurable disease per RECIST v1.1 by blinded independent central review (BICR), and ECOG PS 0 or 1 received pembro 200 mg IV every 3 weeks for up to 35 cycles (~2 years). The primary end point was ORR per RECIST v1.1 by BICR. Secondary end points were DOR, DCR (CR + PR + SD ≥12 wks), and PFS per RECIST v1.1 by BICR; OS; and safety. End points were analyzed in pts who received ≥1 dose of pembro. **Results:** A total of 159 pts were treated with pembro (LA, n = 54; R/M, n = 105). As of September 13, 2023, 33 pts (20.8%) completed treatment and 126 pts (79.2%) discontinued treatment. Median (range) follow-up was 52.4 mo (47.6-56.9) for the LA cohort, 64.7 mo (62.1-69.5) for the R/M cohort, and 63.1 mo (47.6-69.5) in the total population. ORR and DCR are shown in the table. Median DOR (range) was 47.2 mo (1.0+ to 49.9+) in the LA cohort, not reached (NR; 2.7 to 64.2+ mo) in the R/M cohort, and 52.5 mo (1.0+ to 64.2+) in the total population; the proportion of responders with responses ≥12 mo by Kaplan-Meier estimate were 84.8%, 77.8%, and 80.7%, respectively. Median (95% CI) PFS was 14.4 mo (5.5-43.6) in the LA cohort, 5.7 mo (3.1-8.5) in the R/M cohort, and 8.0 mo (5.3-14.4) in the total population; 12-mo rates were 56.7%, 37.3%, and 43.7%, respectively. Median (95% CI) OS was NR (33.3-NR) in the LA cohort, 23.8 mo (13.4-30.9) in the R/M cohort, and 29.8 mo (20.0-42.8) in the total population; 36-mo rates were 62.0%, 39.5%, and 47.0%, respectively. Grade 3-5 treatment-related AEs occurred in 11.3% of pts, and grade 3-5 immune-mediated AEs and infusion reactions occurred in 8.8% of pts. Two pts (1.3%) died due to a treatment-related AE (colitis, cranial nerve disorder). **Conclusions:** With a median follow-up of more than 5 years, pembro continued to show durable responses in pts with LA or R/M cSCC. No new safety signals were observed. Results from this study continue to support the use of pembro in this pt population. Clinical trial information: NCT03284424. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	LA Cohort (n = 54)	R/M Cohort (n = 105)	Total Population (N = 159)
ORR, % (95% CI)	51.9 (37.8-65.7)	35.2 (26.2-45.2)	40.9 (33.2-48.9)
DCR, % (95% CI)	64.8 (50.6-77.3)	52.4 (42.4-62.2)	56.6 (48.5-64.4)
Best overall response, n (%)			
CR	12 (22.2)	13 (12.4)	25 (15.7)
PR	16 (29.6)	24 (22.9)	40 (25.2)
SD of any duration	12 (22.2)	30 (28.6)	42 (26.4)
SD ≥12 wks	7 (13.0)	18 (17.1)	25 (15.7)
PD	9 (16.7)	28 (26.7)	37 (23.3)
NE/NA	5 (9.3)	10 (9.5)	15 (9.4)

9555 Poster Session

Intracranial outcomes with ipilimumab and nivolumab in melanoma brain metastases following progression on anti-PD-1 therapy.

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Background: Ipilimumab + nivolumab (ipi/nivo) is effective for melanoma brain metastases (MBM), but the efficacy of ipi/nivo in MBM in patients (pts) whose melanoma has progressed on anti-PD-1 is unknown. **Methods:** We conducted a retrospective analysis of pts with progressive MBM who received ipi/nivo at Memorial Sloan Kettering Cancer Center following prior anti-PD-1. Cohort A included pts with ≥1 untreated MBM (≥5mm) without local interventions (such as neurosurgery, radiotherapy). Cohort B included pts who had received local interventions for all MBMs before starting ipi/nivo. The primary endpoint was intracranial (IC) progression free survival (PFS). IC response was assessed based on clinical radiological interpretation for Cohort A. Kaplan-Meier methods were used to estimate time-to-event outcomes. **Results:** Fifty-seven pts were identified: 28 and 29 in Cohort A and B, respectively. All pts had received prior anti-PD-1, 42% prior ipi, a median of 2 (IQR: 1, 3) prior lines, and 21% (12/57) of pts prior treatment was in the adjuvant setting only. 79% (45/57) of pts had cutaneous, 14% (8/57) acral, 5% (3/57) unknown primary and 2% (1/57) mucosal melanoma. Median age was 64 (IQR: 58, 71) and 55 (IQR: 47, 70) years in Cohort A and B, respectively. Cohort A had median lesion size (largest measurable MBM) of 1.0cm (IQR: 0.60, 2.12), and 64% (18/28) of pts had >5 lesions; Cohort B had a median lesion size 1.5cm (IQR: 1.10, 2.00) and 28% (8/29) of pts had >5 lesions. 14% (8/57) of pts received concurrent steroid (equivalent of ≥dexamethasone 4mg daily) upon starting ipi/nivo, and leptomeningeal disease was present in 14% (4/28) and 7% (2/29) of Cohort A and B, respectively. The IC response rate was 11% (3/28, 2 were complete (CR)) in Cohort A.Both patients with CR were asymptomatic with ≤ 2 lesions and no prior CTLA-4 exposure. Most (20/28, 71%) in Cohort A had best response of progressive disease (PD); all that had a best response of stable disease (SD; 5/28, 18%) sustained that response for less than 6 months. Median IC-PFS was 1.7 (95% CI: 1.3,4.4) and 7.6 (95% CI: 3.6, -) months, and median overall survival (OS) was 6.7 (95% CI: 3.6,10) and 24 (95% CI: 11, -) months in Cohort A and B. 24-month OS was 19% (95% CI: 8.1,45) and 51% (95% CI: 35,75) in Cohort A and B. 30% (8/27) and 66% (19/29) of pts had subsequent systemic therapy, and 48% (13/27) and 52% (15/29) subsequent local therapy in Cohorts A and B. **Conclusions:** Ipi/nivo has limited efficacy in patients with progressive MBM post-PD-1 therapy in the absence of local therapy. These results highlight the unmet clinical need for more effective therapies to address progressive MBM post-PD-1 therapy, an increasingly relevant clinical scenario particularly in light of the growing use of adjuvant and neoadjuvant anti-PD-1. Research Sponsor: None.

Melphalan/hepatic delivery system versus best available care in patients with unresectable metastatic uveal melanoma: Randomized FOCUS trial results.

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Background: Metastatic uveal melanoma (mUM) has a poor prognosis, with liver metastases typically presenting a therapeutic challenge. Melphalan/Hepatic Delivery System (melphalan/HDS) is a drug/medical device combination used for liver-directed treatment of unresectable mUM patients. The purpose of the FOCUS study, an open label, multicenter randomized Phase 3 study, was to assess efficacy and safety of melphalan/HDS versus best alternative care (BAC). **Methods:** Eligible patients with unresectable mUM were randomized 1:1 to treatment with melphalan/HDS (3.0 mg/kg ideal body weight) once every 6-8 weeks for a maximum of 6 cycles or BAC. The primary endpoint was overall survival (OS). The planned study size was 240 patients; due to slow enrollment and patient reluctance to receive BAC treatment, the study design was amended to a single-arm melphalan/HDS study, and all efficacy analyses of the randomized study were treated as exploratory. **Results:** From February 2016 to October 2018 a total of 129 patients were screened and 85 were enrolled at 22 centers in the US and Europe; eligible patients were randomized to receive melphalan/HDS (N=43) or BAC (N=42) and 72 patients received study treatment. Exploratory analyses of efficacy endpoints showed numerical differences consistently favoring the melphalan/HDS arm vs. BAC (median OS: 18.5 vs 14.5 months; median progression free survival: 9.1 vs 3.3 months; objective response rate: 27.5% vs 9.4%; and disease control rate: 80.0% vs 46.9%). Serious adverse events (SAEs) occurred in 51.2% of melphalan/HDS and in 21.9% of BAC patients. Most common (>5%) SAEs included thrombocytopenia (19.5%), and neutropenia (9.8%), leukopenia (9.8%) and febrile neutropenia (7.3%) in melphalan/HDS patients and cholecystitis, nausea and vomiting (6.3% each) in BAC patients. No treatment-related deaths were observed. **Conclusions:** Treatment with melphalan/HDS shows clinically meaningful efficacy and demonstrates a favorable benefit-risk profile in patients with unresectable mUM as compared to best alternative care. Clinical trial information: NCT02678572. Research Sponsor: Delcath Systems, Inc.

9557 Poster Session

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

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Background: An ITC comparing NIVO + RELA and NIVO + IPI, approved dual immunotherapy treatment options for patients with advanced melanoma, was previously conducted using pt-level data from the pivotal RELATIVITY-047 (RELA-047; NIVO + RELA vs NIVO) and CheckMate 067 (CM-067; NIVO + IPI or NIVO vs IPI) trials (Schadendorf 2023). Here we present results using updated, 3-year follow-up data from RELA-047. **Methods:** Inverse probability of treatment weighting was used to adjust for cross-trial imbalances in baseline characteristics. Database locks were selected to best align follow-up length in RELA-047 (median 34 mo) and CM-067 (median 38 mo). Progression-free survival (PFS) per investigator, confirmed objective response rates (ORRs) per investigator, overall survival (OS), melanoma-specific survival (MSS), treatment-related adverse events (TRAEs), and TRAEs leading to discontinuation (DC) were analyzed. PFS, OS, and ORR were evaluated across key subgroups. PFS, OS, and MSS were compared using Kaplan–Meier curves and hazard ratios (HRs); ORRs were compared using odds ratios (ORs). The weighted NIVO arm from each trial was compared for internal validation. **Results:** After weighting, key baseline characteristics were balanced for NIVO + RELA (n=339) and NIVO + IPI (n=297). Efficacy outcomes after weighting were similar between NIVO + RELA and NIVO + IPI and between NIVO arms (table). Similar outcomes between the NIVO arms validate the ITC methodology. Across subgroups, efficacy appeared similar between treatments, although trends favoring NIVO + IPI were observed for ORR among pts with BRAF MT disease or lactate dehydrogenase $>$ 2x the upper limit of normal. TRAEs were less common with NIVO + RELA (23%) compared to NIVO + IPI (61%); any-grade TRAEs leading to DC occurred in 17% and 41% of pts, respectively. **Conclusions:** Consistent with previous results, this updated ITC suggests that 1L treatment with NIVO + RELA may have comparable efficacy to, and lower toxicity than, NIVO + IPI in pts with advanced melanoma. Results should be interpreted with caution given differences in study designs and changes in treatment landscape. Research is ongoing to determine which pts respond best with each combination. Research Sponsor: Bristol Myers Squibb.

After weighting.

	NIVO + RELA (n = 339) Median, mo (95% CI) / %	NIVO + IPI (n = 297) Median, mo (95% CI) / %	HR/OR (95% CI)	NIVO RELA-047 (n = 338) Median, mo (95% CI) / %	NIVO CM-067 (n = 288) Median, mo (95% CI) / %	HR/OR (95% CI)
PFS per INV	12.0 (8.2–17.1)	11.2 (8.5–18.1)	1.08 (0.88–1.33)	6.7 (4.6–10.2)	5.7 (3.9–9.1)	0.93 (0.77–1.13)
Confirmed ORR per INV	48	50	0.91 (0.73–1.14)	40	40	1.03 (0.81–1.31)
OS	NR (38.6–NR)	NR (37.1–NR)	0.94 (0.75–1.19)	35.1 (28.1–50.5)	35.7 (26.4–NR)	0.97 (0.78–1.21)
MSS	NR (NR–NR)	NR (NR–NR)	0.86 (0.67–1.12)	54.4 (34.7–NR)	NR (32.3–NR)	0.92 (0.73–1.17)

NR: not reached; HR/OR are NIVO+RELA vs NIVO+IPI.

9558 Poster Session

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

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Background: Multiple studies support that the gut microbiome plays a key role in response to ICB. Habitual high dietary fiber intake is associated with improved response to ICB and high fiber diet interventions have been shown to favorably modulate the microbiome in non-cancer populations. We therefore conducted a randomized trial of HFDI versus healthy control diet in melanoma pts receiving ICB. **Methods:** 45 melanoma pts starting ICB (21 adjuvant, 12 neo-adjuvant, 12 advanced unresectable) were enrolled. Pts were randomized 2:1 to HFDI (30 to 50 g/day by ramp-up) or control (20 g) stratified by BMI and treatment (tx) intent. Inclusion criteria included BMI 18.5-40 kg/m2 and willing to exclusively eat the provided diet. Exclusion criteria include diabetes, major gastrointestinal disease/surgery, probiotic, antibiotic, or steroid use within 14 days, smoker or heavy drinker, and average dietary fiber intake $>$ 20g/day. As a controlled feeding study, the weekly menu in both arms were isocaloric (matched to patient's energy needs via 30% fat, 50% carbohydrates, 20% protein) and provided by MD Anderson Bionutrition Research Core for up to 11 weeks. Both diets followed cancer prevention recommendations with little to no processed meats or added sugars; no alcohol consumption; and dietary fiber intake scaled through whole, plant foods. Blood and stool samples were collected longitudinally. Compliance was defined by the proportion of calories consumed vs. provided. **Results:** 65 pts were consented. 20 pts (31%) screen failed largely due to current fiber intake $>$20 g/day. 45 pts were randomized, and 44 pts have completed the study to date. ICB tx were PD1 monotherapy (n=22), ipilimumab + nivolumab (n=16), and nivolumab + relatlimab (n=7). 53% of pts were female and average BMI was 29.7 kg/m^2. Average baseline fiber intake was 15.5 g/day. Compliance with the diet while on study was 83% (95% CI 79%-87%); however, 15 pts (33%) withdrew consent early due to challenges with adherence to the study. The rate of diet-related AEs was 45%, all Grade I/II including abdominal pain (11%), anorexia (5%), bloating (6%), constipation (18%), diarrhea (23%), flatulence (18%), hyperglycemia (2%), nausea (2%) and weight loss (9%). The rate of Grade III/IV immune related adverse events was 25%. **Conclusions:** In this fully-controlled feeding study among melanoma pts undergoing ICB tx, both arms of the intervention were well-tolerated. In contrast to our prior studies in cancer survivor populations, we noted a significant discontinuation rate, perhaps due to the challenges of participating in a fully-controlled feeding study while undergoing active cancer therapy. Ongoing analyses are interrogating the effects of the dietary intervention on the structure and function of the gut microbiome, circulating and stool metabolites, and systemic and anti-tumor immunity. Clinical trial information: NCT04645680. Research Sponsor: MD Anderson Melanoma Moonshot; The Elkins Foundation; Seerave Foundation; The Mark Foundation for Cancer Research; Rising Tide Foundation.

9559 Poster Session

Lenvatinib (len) plus pembrolizumab (pembro) in patients with advanced melanoma that progressed on anti–PD-(L)1 therapy: Over 4 years of follow-up from the phase 2 LEAP-004 study.

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Background: PD-1 inhibitors such as pembro are a standard-of-care option for advanced melanoma, and effective treatments are needed for disease that progresses on anti–PD-(L)1–based therapy. Previous results from the single-arm, open-label, phase 2 LEAP-004 study (NCT03776136) showed that len + pembro had antitumor activity in patients (pts) with advanced melanoma that progressed on prior anti–PD-(L)1–based therapy. With a median follow-up of 15.3 mo, the ORR was 21.4% and median DOR was 8.3 mo. Results from LEAP-004 led to the inclusion of len + pembro in treatment guidelines for pts with advanced melanoma and confirmed progression on a PD-(L)1 inhibitor. Here, we present results from LEAP-004 with over 4 years of follow-up. **Methods:** Eligible pts were aged ≥18 years, had unresectable stage III or IV melanoma, had ≥1 measurable lesion, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had confirmed disease progression within 12 weeks of the last dose of anti–PD-(L)1 therapy given alone or in combination for ≥2 doses. All pts received len 20 mg PO QD + ≤35 doses of pembro 200 mg IV Q3W. The primary end point was ORR per RECIST v1.1 by BICR. Secondary end points included DOR and PFS per RECIST v1.1 by BICR, OS, and safety. **Results:** 103 pts were enrolled and received treatment. Median time from first dose to data cutoff (Oct 11, 2023) was 52.0 months (range, 48.8-55.7). ORR in the overall population was 24.3% (95% CI, 16.4-33.7), with 5 pts (4.9%) having a complete response and 20 (19.4%) a partial response. In key subgroups, ORR was 33.3% (10/30; 95% CI, 17.3-52.8) in pts with progression on prior anti–PD-1 + anti–CTLA-4 therapy and 10.7% (3/28; 95% CI, 2.3-28.2) in pts with *BRAF*-mutant tumors who received prior BRAF/MEK-directed therapy for metastatic disease. Median DOR in the overall population was 8.5 mo (range, 3.2-40.8) and an estimated 35% of responders remained in response at ≥12 mo. Median PFS was 4.2 mo (95% CI, 3.5-6.3); 24-mo PFS rate was 10.1%. Median OS was 14.0 mo (95% CI, 10.8-18.3); 24-mo OS rate was 29.7%. Efficacy outcomes in pts with mucosal (n = 11) and acral lentiginous (n = 8) melanoma were consistent with the overall population. Any-grade treatment-related AEs occurred in 99 pts (96.1%). Grade 3-5 treatment-related AEs occurred in 51 pts (49.5%). No new treatment-related deaths occurred since prior analysis (1 pt had died because of treatment-related decreased platelet count). **Conclusions:** With over 4 years of follow up, len + pembrocontinued to show antitumor activity in pts with advanced melanoma and confirmed progression after ≥2 doses of anti–PD-(L)1-based therapy. Safety remained consistent with previous reports, with no new or unexpected safety signals. These results support len + pembro as a potential treatment option for advanced melanoma after anti–PD-(L)1-based therapy. Clinical trial information: NCT03776136. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Eisai Inc., Nutley, NJ.

The efficacy and safety of toripalimab combined with anlotinib in the first-line treatment of Chinese patients with metastatic melanoma.

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Background: Acral, mucosal and non-CSD melanoma are the major subtypes in Chinese melanoma patients, with poor response to antiprogrammed cell death-1 (PD-1) monotherapy. Anti PD-1 monoclonal antibodies combined with anti-angiogenesis agent have showed synergistic effects mechanically and a promising response rate. Here, we report efficacy and safety of toripalimab combined with anlotinib in Chinese patients with metastatic melanoma. **Methods:** Patients with metastatic acral, mucosal and non-CSD melanoma received toripalimab 240mg intravenously every 3 weeks combined with anlotinib 12 mg orally once a day for first 2 weeks every 3 weeks as first-line treatment, until disease progression or unacceptable toxicity. All patients were enrolled from the Cancer Center of Union Hospital, affiliated to Tongji Medical College of Huazhong University of Science and Technology and Hunan Cancer Hospital. **Results:** From January 2021 to January 2024, a total of 47 patients were enrolled in this study. Subtypes were 16 patients with acral melanoma, 21 patients with mucosal melanoma, and 10 patients with non-CSD melanoma. Average age was 59.7 ±10.1 years old. The median follow-up was 26.5 months (95% *CI:* 20.6, 32.4 months). Among the 46 efficacy evaluable patients, the objective response rate (ORR) and disease control rate (DCR) were 23.9% and 80.4%, respectively. Median duration of response was 14.4 months (95% *CI:* 7.5, 21.3). The median progression-free survival (PFS) of all 47 patients was 5.7 months (95% CI 4.2 to 7.2 months); and the median OS was 14.4 months (95% CI 7.3 to 21.5 months). The median PFS of patients with M1a stage is 24.4 months, statistically longer than M1b (5.1 months), M1c (6.6 months) and M1d (4.0 months). The median PFS of acral, mucosal and non-CSD melanoma were 6.6m, 5.1m, 5.2m respectively with no statistical difference, and these is no difference of PFS between gender and age. In terms of safety, treatment-related adverse events (TRAEs) for all grades occurred in 76.6% (36/47) of patients, and grade 3 or 4 occurred in 4.3% (2/47) of patients. The incidence of immune-related adverse reactions (irAE) was 23.4% (11/47) for all grades, the most common irAEs (≥2%) included hypothyroidism, immune-associated hepatitis and rash. **Conclusions:** Toripalimab combined with anlotinib displays good efficacy and well-tolerant safety profiles in the treatment of patients with metastatic melanoma. Further biomarker analysis was ongoing. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation.

9561 Poster Session

Immunogenicity of an AI-designed personalized neoantigen vaccine, EVX-01, in combination with anti-PD-1 therapy in patients with metastatic melanoma.

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Background: Personalized vaccines, targeting mutation-derived neoantigens (neoAg), represent a promising frontier in cancer immunotherapy. Here, we characterize the vaccine-induced immune response in seven melanoma patients treated with the AI-generated personalized cancer vaccine, EVX-01, in the ongoing single arm multicenter trial (NCT05309421). Data from an additional five patients will be available at the time of presentation. **Methods:** Tumor-specific neoAgs were identified and selected using the proprietary vaccine target discovery AI-Immunology platform based on tumor DNA- and RNA-sequencing data. The top-ranked neoAgs for each patient were manufactured as synthetic long peptides and formulated with an adjuvant, creating the personalized cancer vaccine, EVX-01, tailored to the individual tumor and immune system characteristics. Patients initiated anti-PD1 therapy (Pembrolizumab) 12 weeks prior to EVX-01 administration. Each patient received six priming doses of EVX-01 administered bi-weekly and will be followed by four booster immunizations at later timepoints. Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples collected at different timepoints to evaluate the effect of anti-PD1 therapy, EVX-01 priming immunizations and EVX-01 booster immunizations on T-cell immunogenicity. NeoAg-specific T-cell responses were evaluated by IFN-γ ELISpot assay and intracellular cytokine staining after T cell in vitro expansion with vaccine neoAgs. **Results:** Immunogenicity analysis of PBMC samples from seven patients demonstrated that EVX-01 induced neoAg-specific immune responses in all patients after the priming phase. The effect of booster immunizations on neoAg-specific T-cell responses was analyzed in the patients who had reached these late visits of the study, and it demonstrated a clear trend towards increased immune responses after the first booster dose. The observed responses were mediated by both CD4+ and CD8+ neoAg-specific T-cells. Investigations of the response induced by the individual vaccine neoAgs revealed that the majority of the EVX-01 neoAgs triggered a specific T-cell response, affirming the ability of the AI-Immunology™ platform to precisely select effective vaccine targets. Data from an additional five patients will be available at the time of presentation. Importantly EVX-01 was safe and well-tolerated, with only grade 1 and 2 ADRs related to EVX-01 even after boosting. The combination of EVX-01 and anti-PD1 also appeared safe and well tolerated. **Conclusions:** EVX-01 induced neoAg-specific immune responses in all analyzed patients and a broad response against the neoAgs. These results further validate the precision and predictive power of our proprietary vaccine target discovery AI-Immunology platform. The combination of EVX-01 and anti-PD1 was safe and well tolerated. Clinical trial information: NCT05309421. Research Sponsor: None.

9562 Poster Session

First-in-class PD-1/IL-2 bispecific antibody fusion protein IBI363 in patients with advanced melanoma: Safety and efficacy results from a phase I study.

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Background: Despite great success of immunotherapy (IO) in advanced melanoma, there remains unmet clinical needs for IO resistant and cold tumors. IBI363 is a first-in-class PD-1/IL-$2^{\alpha\text{-bias}}$ bispecific antibody fusion protein which could block PD-1 checkpoint and activate α-bias IL-2 to rejuvenate exhausted tumor-specific T cells. Herein, we report updated results from the phase I study to evaluate safety and efficacy of IBI363 in pts with advanced melanoma. **Methods:** Eligible pts with advanced melanoma who failed or intolerant to standard therapy were enrolled to receive IBI363 intravenously at different dose levels ranging from 100-2000 μg/kg QW/Q2W/Q3W. Primary objective of the study was safety. Secondary objective was efficacy assessed by investigator per RECIST v1.1 including objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression free survival (PFS). **Results:** As of January 11, 2024, 67 pts were enrolled (females: 55.2%, median age: 59.0 years, ECOG PS 1: 74.6%, prior treatment lines ≥2: 59.7%, prior IO: 89.6%). There were 17 pts with cutaneous melanoma, 22 pts with acral melanoma, 25 pts with mucosal melanoma and 3 pts with unknown primary melanoma. The median treatment duration was 12.0 weeks (range: 2.0-43.6) with 38 pts (56.7%) still on treatment. Most comment reason for end of treatment was disease progression in 25 pts (37.3%). All pts were included in safety analysis. Treatment-emergent adverse events (TEAEs) occurred in 63 (94.0%) pts. Grade ≥3 TEAEs and TRAEs occurred in 16 (23.9%) and 12 (17.9%) pts. Common TEAEs (≥20%) were arthralgia (34.3%), hyperthyroidism (29.9%), anemia (25.4%). TEAE leading to treatment discontinuation occurred in 1 (1.5%) pt.No pts had TEAEs leading to death. Pts with at least 1 post-baseline tumor assessment were included in efficacy evaluable set. In all evaluable pts (n=57), the best overall response was partial response (PR) in 16 pts, stable disease (SD) in 25 pts and progressive disease (PD) in 16 pts. The overall ORR was 28.1% (95%CI: 17.0-41.5%) and DCR was 71.9% (95%CI: 58.5-83.0). In pts had prior IO (n=52), ORR was 21.2% (95%CI: 11.1-34.7) and DCR was 67.3% (95%CI: 52.9-79.7). In 1 mg/kg Q2W pts had prior IO (n=25), ORR was 32.0% (95%CI: 14.9-53.5) and DCR was 80.0% (95%CI: 59.3-93.2). The DoR and PFS data were immature at the time of analysis. Biomarker analysis in baseline tumor region observed significantly higher CD8 T cell infiltration (measured by cell positivity and density) in PR/SD patients than PD patients ($p<0.05$). More updated data on safety and efficacy will be presented at the meeting. **Conclusions:** In pts with advanced melanoma, IBI363 showed encouraging efficacy in different tumor subtypes and in pts wit prior IO. The safety profiles were acceptable and manageable. Further clinical development of IBI363 in melanoma are ongoing both in China and overseas. Clinical trial information: NCT05460767. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

9563 Poster Session

Analyzing the gut microbiome in adolescent and young adult patients with melanoma receiving immune checkpoint blockade.

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Background: Melanoma is the third most common cancer in adolescent and young adults (AYA), a unique cohort defined as patients between 15-39 years of age per the National Cancer Institute. Immune checkpoint inhibitors (ICI) have changed the landscape for advanced melanoma treatment, and the gut microbiota has been shown to remodel the tumor microenvironment to improve ICI efficacy. There is a paucity of research in this cohort, however studies show that AYA patients, in general, have historically not seen the same survival gains as other age groups. Furthermore, literature shows that survival was much worse for AYA's with stage IV melanoma than observed among older adults. **Methods:** The AYA cohort in this retrospective review is from the 2021 Science publication entitled "Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response". This cohort was matched on a 2:1 basis with older non-AYA patients 50-70 years of age. We controlled for sex, BMI, race, treatment naivety, stage of disease, as well as smoking, drug, and alcohol status. **Results:** Our AYA cohort of 23 patients is comprised of 15 females, 22 Caucasians, 20 with primary cutaneous melanoma, 12 with stage III at the start of treatment and 11 with stage IV, 17 were BRAF positive, 8 received combined immunotherapy, 20 were treatment naïve, and 11 were responders. We found no difference in alpha or beta diversity in AYA and older non-AYA patients, however alpha diversity increased with age. This is consistent with literature regarding aging gut microbiomes. Furthermore, we noted the most common microbes found between these groups varied considerably. Using differential analyses, we found, for example, a higher abundance of Ruminococcaceae, at the family level, in older non-AYA patients and a higher abundance of *Bacteroides stercoris* in AYA patients. Literature shows the relative abundance of Ruminococcaceae increased with age and was significantly higher in older patients. Furthermore, *Bacteroides stercoris* correlates positively with fiber, grain, and vegetable intake. Additionally, *Blautia massiliensia*, *Blautia obeum*, and *Dorea longicatena* were found to be significantly more prevalent (p=0.010, p=0.34, and p=0.035, respectively)) in older non-AYA patients. These species are all known to be obesity biomarkers. **Conclusions:** We found that the gut microbiota of AYA and older non-AYA melanoma patients differ. Older non-AYA patients have bacterial species associated with negative biomarkers which may be due to an aging gut microbiome. Establishing microbial features in the AYA population can help with microbiome modulation as a therapeutic strategy. Enriching modalities include fecal microbiota transplantation, probiotics, and improving diet as well as fiber intake. Further research should explore if the gut microbiome influences worse outcomes in AYA's with late stage melanoma.
Research Sponsor: None.

9564 Poster Session

Association between circulating tumor DNA (ctDNA) and recurrence-free survival (RFS) in patients (pts) with resected stage III melanoma: An exploratory analysis of SWOG S1404.

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Background: Our exploratory study aimed to understand the association between the presence of ctDNA after definitive surgical resection and RFS in pts with stage III melanoma treated with adjuvant immunotherapy. **Methods:** This study included 92 pts with resected stage III melanoma enrolled in a phase 3 trial (NCT02506153) that evaluated the efficacy of adjuvant pembrolizumab compared to interferon alfa-2b or ipilimumab in pts with stage IIIA(N2a)-IV resected melanoma. Personalized, tumor-informed ctDNA assays (Signatera) were run on banked plasma samples (median: 3.8 mL) collected at up to 5 time points after resection: pre-adjuvant treatment (pre-Tx), 1, 3, 6, or 12 months after Tx initiation and at recurrence. RFS was measured from randomization (pre-Tx) to first recurrence or death. A case-control design was used: 50% with recurrence within 2 yrs of randomization and 50% alive without recurrence for $>$ 2 yrs. Conditional logistic regression compared the presence of ctDNA at pre-Tx between case-control groups. **Results:** Of the 92 pts, samples from 10 did not pass quality control. This study analyzed a total of 245 plasma samples from 82 pts. No significant differences in demographics, including stage, number of + lymph nodes, and BRAF status, existed between pts who were ctDNA+ or ctDNA- pre-Tx. 7 of 10 pts (70.0%) who were ctDNA+ pre-Tx had disease recurrence within 2 yrs compared to 33 of 72 pts (45.8%) who were ctDNA- ($p = 0.19$). 2-yr RFS was 30% in pts who were ctDNA+ pre-Tx and 54% in pts who were ctDNA- (HR 1.75; 95% CI: 0.78, 3.94; $p = 0.18$). Of the 7 pts who were ctDNA+ pre-Tx and had disease recurrence within 2 yrs, 5 were ctDNA+ at all time points assessed. The other 2 pts transiently cleared ctDNA during Tx, turning back ctDNA+ prior to recurrence. Of the 3 pts who were ctDNA+ pre-Tx and did not recur within 2 yrs, 2 cleared ctDNA during immunotherapy and remained ctDNA- at later time points. All 39 pts who were ctDNA- pre-Tx and did not recur within 2 yrs remained ctDNA- at later time points. Among 29 pts having ctDNA timepoints available for analysis near the time of recurrence (end-of-Tx or on-progression timepoints), 22 (75.9%) were ctDNA+. **Conclusions:** In this study, pre-Tx incidence of ctDNA+ after surgical resection was low, potentially related to limited plasma yield. However, the ctDNA positivity rate increased in subsequent serial testing. ctDNA might help identify early disease recurrence in patients with melanoma in the adjuvant setting, but further studies of larger cohorts accounting for treatment effect with more uniform pre-analytic collection are needed. Research Sponsor: NIH/NCI/NCTN grants U10CA180888, U10CA180819, CA180820, CA180863; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

9565 Poster Session

Prediction of melanoma metastasis using dermatoscopy deep features: An international multicenter cohort study.

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Background: Machine learning algorithms, and especially convolutional neural networks, demonstrated modest accuracy on the prediction of melanoma metastasis, based on histological images and clinicopathological information. Whether dermatoscopy deep features could serve as biomarker for the prediction of melanoma metastasis, remains an underexplored area in medical research. **Methods:** An international, multicenter, cohort study of cutaneous melanoma patients from 3 different continents was conducted. Patients with cutaneous melanoma, who had available clinical and dermatoscopic images and an adequate follow-up time for the development of metastasis (both locoregional and distant) were included. We utilized a support vector machine (SVM) classifier, to distinguish between melanomas that metastasized and those that did not. We used a pre-trained ResNet 50 network, we separated dataset into training set and testing set, stratified by TNM-stage, and to ensure robustness and guard against biased data selection, the stratified split into training and testing sets was repeated five times, resulting in five different training-test sets. The primary outcome was the comparison of the prognostic performance of deep dermatoscopy features based on SVM (model 1) to the performance of established prognostic factors of melanoma, such as Breslow thickness and ulceration (model 2) and to a combined model using deep features and histopathologic factors (model 3). A secondary aim was to examine the diagnostic performance of model 1 in stage IIB and IIC patients at diagnosis. The prognostic performance was assessed using the Area Under the Curve (AUC) and the True Positive Rate (TPR) at a True Negative Rate at 70%. **Results:** 712 patients were included, 465 (65.3%) non-metastatic and 247 (34.7%) metastatic, within a median follow-up of 60 months. The SVM model demonstrated mean AUC 0.84 (95% CI 0.80 – 0.87) and TPR 0.81 (95%CI 0.73 – 0.90). Similar results were shown for model 2 and model 3, and no statistically significant differences among models were detected in terms of AUC (De Long's test, $p>0.05$ and ANOVA Kruskal-Wallis $p>0.05$). Regarding IIB/IIC patients and combining data from five test sets, SVM correctly classified as metastatic 21 out of 23 (91.3%) stage IIB and 21 out of 23 (91.3%) stage IIC patients, who eventually developed metastasis during follow-up. **Conclusions:** Our findings suggest that dermatoscopy deep features could offer an immediate, in vivo prediction of melanoma metastasis prior to excision. This advancement holds significant clinical importance, prioritizing high-risk patients for neoadjuvant treatment or guiding selection of patients who might benefit from adjuvant therapy. Research Sponsor: None.

9566 Poster Session

Neoadjuvant pembrolizumab plus lenvatinib in patients with resectable stage III melanoma (NeoPele): Analysis of tumor microenvironment (TME) correlated to pathological response.

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Background: The phase II SWOG S1801 study showed an improved event-free survival with anti-PD-1 (PD1) neoadjuvant immunotherapy (neoIT) vs adjuvant PD1. One hypothesis explaining this benefit is the presence of tumor-draining lymph nodes (tdLN; defined as the nearest node to the tumor without direct involvement) as a potential reserve of stem-like (TCF7+) T cells, crucial to a good response to IT. We sought to analyze the immune infiltrate of the tumor-involved LN (ie TME) and tdLN from patients (pts) achieving major pathological response (MPR: complete [pCR] or near-complete [near-pCR] pathological response) vs non-MPR (partial [pPR] or no [pNR] pathological response). **Methods:** Pts with stage III melanoma treated with 6 weeks of PD1-based neoIT (PD1 + Lenvatinib) were included (NeoPele clinical trial; NCT04207086). Multiplex fluorescent immunohistochemistry of the TME before and after neoIT, and of the tdLN after neoIT was analyzed (T cell panel: CD3, TCF7, CD103, FoxP3, CD39 and Sox10; and B cell panel: CD20, CD21, CXCR5, TCF7, CD3 and SOX10). Lymphoid aggregates, characterized by clusters of CD21+ and CXCR5+ immune cells, were quantified. **Results:** Of the 20 pts, 11 (55%) had MPR (8 [40%] with pCR and 3 [15%] with near-pCR) and 9 (45%) had a non-MPR (4 [20%] with pPR and 5 [25%] with pNR). At baseline, MPR pts had a higher % of T cells (11% vs 3%, p = 0.0127) and follicular B helper T cells (CXCR5+; 29% vs 9%, p = 0.0293) than non-MPR pts in the TME. NeoIT led to an increase in the % of T cells, mainly in pts with MPR (median +30%; p = 0.0156) vs non-MPR (median +7%; p = 0.0312) pts, including an increase in the % of tumor-reactive (CD39+) T cells (p = 0.0195), but a decrease in % of tissue-resident stem-like (CD103+ TCF7+) T cells (p = 0.0195). Within the B cell compartment, there was an increase in the % of CD21+ B cells and mature (CD21+ CXCR5+) B cells in MPR vs non-MPR pts. At week 6, MPR pts maintained a higher % of T cells (36% vs 11%, p = 0.0172), follicular B helper T cells (20% vs 9%, p = 0.0133), and mature B cells (10% vs 2%, p = 0.0021) in the TME compared with non-MPR. NeoIT led to a significant increase in the number of lymphoid aggregates in the TME from MPR pts (median +42; p = 0,0156), but no difference in non-MPR pts. No differences were observed in the tdLN based on pathological response. **Conclusions:** MPR pts had a higher density of T cells in the TME at baseline, and a more differentiated and activated immune profile after neoIT compared with non-MPR pts. MPR pts had a significant increase in the number of lymphoid aggregates at week 6 compared to non-MPR pts; however, the role of these lymphoid aggregates, including the follicular B helper T cell subset and mature B cells, promoting a good pathological response to neoIT is yet to be clarified. Clinical trial information: NCT04207086. Research Sponsor: MSD.

Correlation of eTILs with recurrence free survival (RFS) in stage IIB-IIIA melanoma and use as biomarker for stratification for clinical trials.

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Background: Immunotherapy is approved for resected stage IIB-IIIC, but treatment of all patients, particularly those with IIB-IIIA disease, incurs unneeded expense and toxicity. Biomarkers are urgently needed for patient stratification. Time constraints in clinical trial design have led to the adoption of recurrence free survival (RFS) as a primary endpoint in adjuvant melanoma trials. Tumor infiltrating lymphocytes (TILs) are a well-established biomarker in primary melanoma, but quantification is subjective. Electronic TILs (eTILs) are a previously published automated digital pathology tool to quantify TILs. **Methods:** A retrospective cohort of 194 patients with Stage II-III melanoma from Roswell Park Comprehensive Cancer Center (RPCCC, n=133) and Geisinger Medical Center (GMC, n=61) were evaluated for eTILS by blinded investigators. Patients were included based on a search of dermatopathology databases and tissue availability. Digital images of diagnostic slides were analyzed using quPath, a publicly available software. Briefly, tumor areas were selected to include infiltrating lymphocytes with minimal adjacent stroma. Color variations in H&E images were standardized, and cell types quantified utilizing a machine learning algorithm. A previously published threshold of 16.6% eTILs, calculated as lymphocytes/tumor cells x 100, was used. Patients were staged using American Joint Committee on Cancer (AJCC) guidelines, version 8. Survival was assessed using Kaplan-Meier Curves and correlation of clinic-pathologic features with survival was tested using Cox Proportional Hazards Models. **Results:** Of 194 patients, 56 were stage IIA, 85 were IIB-IIIA, and 53 were IIIB-D. Median follow up was 47.5 months. 103 patients had eTILs >16.6% of whom 13 (12.6%) died and 84 had eTILS <16.6% of whom 23 (27.4%) died during follow-up. HR for death from melanoma within 5 years for the high eTIL group was 0.53 (CI 0.21-0.90, p=0.024). DSS was significantly longer in the high eTIL group than the low eTIL group (p=0.0095). Among 85 stage IIB-IIIA patients, local and distant recurrence data was available for the RPCCC cohort of 68 patients. 46 of these patients had high eTILs of whom 9(19.6%) recurred and 22 had low eTILS of whom 10 (45.95%) recurred. HR for recurrence within 5 years for the high eTIL group was 0.44 (CI0.23-0.83, p=0.012). RFS was significantly longer in the high TIL group (p=0.016) as was distant metastatic recurrent survival (p= 0.0063). eTIL score correlated with RFS in a univariable Cox model (p=0.033) and added to stage and depth in a multivariable Cox model (p=0.018). **Conclusions:** eTILs, readily evaluable at low cost using diagnostic slides, correlate with clinical outcome in a retrospective cohort of 194 patients. eTILS should be prospectively evaluated as a biomarker to stratify early-stage melanoma patients for adjuvant clinical trials. Research Sponsor: National Cancer institute-NIH.

9568 Poster Session

A prognostic model based on selected cell state and cellular community scores in patients with advanced melanoma treated with immune checkpoint inhibitors (Ecotype-ICI score) as a predictor of ICI immunotherapeutic benefits.

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Background: We conducted an enhanced immune cell state atlas analysis of the data of patients with melanoma treated with ICI to investigate predictors of therapeutic benefits and mechanisms of resistance. **Methods:** Leveraging RNA-seq from melanoma patients (n=141) treated with ICI within the ORIEN Avatar project (NCT03977402), we constructed a prognostic model based on selected cell state and cellular community scores, also known as ecotype-ICI score (*Li. AACR 2023*). We evaluated the model's predictive value using transcriptomic data from high-risk melanoma patients treated with adjuvant ipilimumab (n=471) or interferon-α (n=248) as part of the E1609 phase 3 trial (1). RNA-seq data were initially deconvoluted for cellular community signatures using EcoTyper. The six prognostic carcinoma ecotype (CE) signatures identified (CE1, CE2, C6, CE7, CD9, CD10) were utilized for calculating a risk score based on a multivariable Cox model, which was trained using Avatar data. For additional external validation, we analyzed data from patients with metastatic melanoma treated with anti-CTLA4 (*Va.* n=40), anti-PD1 (*Liu.* n=121), and anti-PD1 alone or combined with anti-CTLA4 (*Gide.* n=66). A series of ad hoc survival analyses, including Kaplan-Meier analysis, log-rank tests, and Cox regression were further applied. **Results:** The ecotype-ICI score showed strong prognostic significance in predicting overall survival (OS) in the entire group of E1609 patients (N=719; Cox $P < 0.0001$, log-rank $P < 0.0001$), the ipilimumab cohort (Cox $P < 0.000143$, log-rank $P = 0.00011$), but less so with interferon (Cox $P = 0.06$). CE9, characterized by its proinflammatory nature and IFN-gamma signaling, and CE10, noted for its canonical T cell state signatures, both demonstrated a leading predictive value according to multivariable Cox regression analysis. Interestingly, CE2, noted for its lymphocyte deficiency signature, also demonstrated complementary predictive value for outcomes following ipilimumab. Within the validation cohorts of public data sets noted above, the ecotype-ICI scores showed similarly strong prognostic significance in predicting OS (Gide. $P = 0.045$; Liu. $P = 0.029$; Va. $P = 0.011$). Ecotype-ICI also demonstrated a distinct distribution in the responder group (complete or partial response) compared to the progressive disease group, underscoring its potential as a discriminative biomarker for ICI response and survival outcomes. **Conclusions:** Our analysis has successfully established the utility of the immune cell state atlas in predicting therapeutic benefits with ICIs across diverse ICI treatment regimens in melanoma. We will update our results with data related to gene ontology, KEGG pathways and the most complementary pathway signatures at the meeting. 1. Tarhini, 2020. Research Sponsor: ORIEN Foundation and Community Foundation of Tampa Bay.

9569 Poster Session

Immune phenotype profiling based on anatomic origin of melanoma and impact on clinical outcomes of immune checkpoint inhibitor treatment.

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Background: The inflamed immune phenotype is associated with a favorable response to immunotherapy in metastatic malignant melanoma. Although variations in molecular features across melanoma subtypes and differing ethnic distributions have been well reported, studies investigating immune phenotypes across multiple institutions within the context of different melanoma subtypes are scarce. We examined the association of immune phenotypes with outcomes after immunotherapy, based on subtypes of malignant melanoma. **Methods:** Two institutional advanced melanoma cohortsrepresenting Asian and Western populations (YUHS, n = 123; Stanford University, n = 102) were included. H&E-stained tumor slides were assessed using Lunit SCOPE IO, an AI-powered whole slide image analyzer, to define the inflamed score (IS, % of inflamed area) and the inflamed phenotype (>33.3% IS). Clinical outcomes after immune checkpoint inhibitor (anti-PD-1/PD-L1) treatment, including progression-free survival (PFS) and overall-survival (OS), were assessed. **Results:** In the overall cohort (n = 225), the inflamed phenotype was associated with prolonged PFS (HR = 0.634, 95% CI: 0.453 – 0.887, p = 0.007) and OS (HR = 0.655, 95% CI: 0.432 – 0.992, p = 0.044). On analysis of melanoma subtypes, we identified non-acral cutaneous melanomas (CM, n = 94), acral melanomas (AM, n = 52), mucosal melanomas (n = 43), uveal melanomas (n = 16), and melanomas of unknown primary site (n = 20), with a disproportionate enrichment of AM (37.4%) and mucosal (29.3%) melanoma cases in the YUHS cohort and CM cases (68.6%) in the Stanford cohort. The IS varied across different melanoma subtypes, with the highest IS observed in CM (median, [IQR]; 34.0, [5.8–52.2]), and significantly lower scores in AM (22.3, [7.7–36.9]), mucosal (13.6, [0–31.4]), and uveal melanoma (5.5, [0–13.6]). Among CM patients, the inflamed phenotype was significantly associated with better post-immunotherapy PFS (HR = 0.476, 95% CI: 0.274 – 0.826, p = 0.007). In contrast, the inflamed phenotype did not correlate with survival in AM patients (p = 0.58), who exhibited universally poorer PFS compared to non-AM patients (HR = 2.124, 95% CI: 1.486 - 3.005). **Conclusions:** AI-powered immune phenotype assessment highlights a heterogeneity of immune phenotypes across specific melanoma subtypes, as well as differential association with outcomes after immune checkpoint inhibitor treatment. While CM patients were well-stratified by immune phenotype, the predictive value of immune phenotyping was less pronounced in acral melanomas, which demonstrated poorer outcomes following immunotherapy. Research Sponsor: None.

Clinical validation of a prognostic 7-marker IHC assay (7-IHC) in 382 patients (pts) with stage IB/IIA cutaneous melanoma (CM; MELARISK-001).

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Background: For pts with resected CM, adjuvant anti-PD1 is approved for AJCC v8 stage IIB–IV and BRAFi/MEKi for stage III–IV disease. Nonetheless, there remains a subgroup of pts within stages IB/IIA, which is at high risk of relapse and death, accounts for a considerable share of overall CM mortality (1), and lacks access to such therapy. Thus, adjuvant clinical trials in this "early"-stage setting may be merited. However, this subgroup is not detectable via AJCC staging alone. A prognostic 7-IHC assay that was developed (2), and analytically (3) and prospectively clinically validated (4) to identify stage IB/IIA pts at high risk of relapse and death, may be useful in selecting pts for adjuvant trials (2,4). Here, we report results from the MELARISK-001 multicenter study of that assay. **Methods:** MELARISK-001 enrolled consecutive pts diagnosed with stage IB/IIA CM from 2000–16, with available formalin-fixed paraffin-embedded primary melanoma. Specimens were analyzed by 7-IHC and pts classified as either high-risk or low-risk. Kaplan-Meier survival analysis and multivariate Cox regression analysis (MVA) against Breslow thickness, ulceration, age, and sex were performed. **Results:** MELARISK-001 included 382 pts; 247 (65%) pts in stage IB, 135 (35%) in stage IIA, all sentinel node-negative. Median Breslow thickness was 1.6 mm, median age 60Y. 212 pts (55%) were classified as 7-IHC high-risk, 170 pts (45%) as 7-IHC low-risk. Median follow-up for recurrence-free survival (RFS) was 90 mos, for melanoma-specific survival (MSS) 98 mos. Comparing 7-IHC high-risk vs low-risk pts, 5Y RFS was 79% vs 100%, 10Y RFS, 72% vs 99%, 5Y MSS, 92% vs 100%, and 10Y MSS 82% vs 100% (Table; logrank $p<0.001$). In MVA, 7-IHC risk class (hazard ratio [HR] 22.3; 95% CI 7.0–70.9), Breslow thickness (1.5; 1.1–1.9), and age (1.61; 1.0–2.5) were significant independent prognosticators of RFS. 7-IHC HR for MSS could not be computed due to 7-IHC's 100% sensitivity. Prognostic performance variables (95% CI) for RFS were: sensitivity 98% (91%–100%), positive predictive value 26% (20%–33%), negative predictive value 99% (97%–100%). **Conclusions:** 7-IHC risk categorization identified 98% of relapses and 100% of CM-related deaths in stage IB/IIA pts. In MVA, 7-IHC risk class was the strongest independent prognosticator of survival endpoints. 7-IHC high-risk pts have a relapse rate comparable to that of later-stage pts for whom adjuvant therapy is approved. MELARISK-001 provides further evidence supporting use of 7-IHC to identify early-stage pts at high risk of relapse and death who may benefit from adjuvant therapy trials. 1. Whiteman et al *J Invest Dermatol* 2015. 2. Meyer et al *PloS ONE* 2012. 3. Ziemer et al *Diagnostics*2023. 4. Meyer et al *Eur J Cancer* 2023. Research Sponsor: None.

			RFS		MSS	
Group		**n (%)**	**5Y**	**10Y**	**5Y**	**10Y**
Overall		382 (100%)	88%	84%	95%	90%
7-IHC	**High-risk**	212 (55%)	79%	72%	92%	82%
	Low-risk	170 (45%)	100%	99%	100%	100%

Adjuvant BRAF/MEK versus anti-PD-1 in BRAF-mutant melanoma: Propensity score–matched recurrence-free, distant metastasis-free, and overall survival analysis.

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Background: Adjuvant BRAF/MEK inhibitors (BRAF/MEKi) and immunotherapy with anti-PD-1 have become the standard of care for resected high-risk stage III and IV melanoma, but a head-to-head comparison is lacking. In our earlier study, we compared adjuvant BRAF/MEKi and anti-PD-1 in a nationwide cohort in the Netherlands. However, the follow-up was too limited for overall survival (OS) analysis. We present an updated analysis including OS with extended follow-up. **Methods:** We included all resected high-risk stage III melanoma patients treated with first-line adjuvant BRAF/MEKi and anti-PD-1 from the Dutch Melanoma Treatment Registry from 2018-2023. We performed a propensity score matched outcome analysis of 1- and 2-year recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and OS. Grade $\geq$ 3 toxicity rates and discontinuation rates due to toxicity were described. **Results:** In total, 225 BRAF/MEKi-treated patients and 729 anti-PD-1-treated patients were included. BRAF/MEKi-treated patients had lower disease stages (16.4% versus 10.2% stage IIIA disease; p=0.01) and more comorbidities (76.0% versus 63.8%; p<0.01) than anti-PD-1-treated patients. Median follow-up duration was 20.9 months. Two similar groups of 213 patients each were created by propensity score matching. Before matching, RFS and DMFS were significantly shorter in the anti-PD-1 treated patients, OS was not (Table). After matching, the 1- and 2-year RFS, DMFS and OS rates were not significantly different (Table). Toxicity data will be presented at the meeting. **Conclusions:** Our results suggest no significant differences in outcomes between adjuvant BRAF/MEKi and anti-PD-1 treatment in stage III melanoma. Research Sponsor: None.

1- and 2-year RFS, DMFS, and OS rates for BRAF/MEK inhibitors and anti-PD-1 in the unmatched cohort (A) and in the matched cohort (B).

	A) BRAF/MEK (n=225)	Anti-PD-1 (n=729)	B) BRAF/MEK (n=213)	Anti-PD-1 (n=213)
1-year RFS rate	83.1% (77.3-89.3%)	71.6% (68.2-75.2%)	83.8% (78.0-90.0%)	76.8% (70.9-83.3%)
2-year RFS rate	66.4% (57.5-76.7%)	61.7% (57.7-66.1%)	66.1% (56.9-76.3%)	70.2% (63.4-77.8%)
P-value	0.04		0.95	
1-year DMFS rate	91.8% (87.6-96.2%)	85.4% (82.7-88.2%)	92.1% (87.8-96.5%)	87.1% (82.3-92.2%)
2-year DMFS rate	84.2% (77.4-91.6%)	78.0% (74.5-81.7%)	84.1% (77.0-91.8%)	81.2% (75.1-87.7%)
P-value	0.05		0.35	
1-year OS rate	93.0% (88.9-97.3%)	96.8% (95.4-98.2%)	92.7% (88.4-97.2%)	97.7% (95.6-100%)
2-year OS rate	81.3% (73.9-89.5%)	87.4% (84.4-90.5%)	80.4% (72.7-89.0%)	85.1% (79.0-91.7%)
P-value	0.75		0.65	

DMFS = distant metastasis-free survival, OS = overall survival, RFS = recurrence-free survival.

9574 Poster Session

Identification of patients at high risk for relapse using the Merlin Assay (CP-GEP) in an independent cohort of 451 patients (pts) with stage I/II melanoma who did not undergo sentinel lymph node biopsy.

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Background: Sentinel lymph node biopsy (SLNB) is the gold standard for nodal assessment in staging cutaneous melanoma (CM) according to AJCC v8 guideline. 80-85% of pts are negative for nodal metastasis, but most pts who relapse or die from melanoma are initially diagnosed as 'low risk' early-stage. Previously we showed that the clinicopathological-gene expression profiling (CP-GEP) model is able to stratify SLNB negative pts for their risk of recurrence (1). Later we showed in a small cohort (n=80) that CP-GEP also has the potential to stratify pts who did not undergo SLNB in low and high-risk of recurrence (2). Here we investigate CP-GEP ability to stratify pts who did not undergo SLNB for their risk of recurrence in an expanded cohort. **Methods:** We analysedformalin-fixed paraffin-embedded primary tumor samples of 451 pts with stage I/II CM diagnosed between 2000-2017, included in the Central Malignant Melanoma Registry, who did not receive SLNB. Study hypothesis and protocol were prospectively formulated. Tumors were analyzed blinded to clinical outcome. The CP-GEP model used combines the expression of 8 genes (*SERPINE2*, *GDF15*, *ITGB3*, *CXCL8*, *LOXL4*, *TGFBR1*, *PLAT* and *MLANA*) by quantitative reverse transcription polymerase chain reaction with age and Breslow thickness to obtain a binary output: CP-GEP Low- or High-Risk. Relapse-free survival (RFS), distant metastasis free survival (DMFS) and Melanoma Specific Survival (MSS) were evaluated using Kaplan-Meier curves. **Results:** We included 451 pts (stage IA-IIC). 40% were females, median age was 63-year-old, median Breslow thickness was 0.5 mm, and the majority were not ulcerated (96%). An interim analysis was performed on samples from 159 pts and showed the following survival: 5-year RFS 85.8%; DMFS 94.1; MSS 95.7%. The median follow-up time of 57 months (RFS). CP-GEP identified 149 pts as Low-Risk and 10 pts as High-Risk. The 5-year RFS rate was 90.5% and 0% (HR 23.85; $p < 0.001$), 5-year DMFS was 97.2% and 27% (HR 43.14; $p < 0.001$), respectively for CP-GEP Low-Risk and High-Risk pts. The 5-year MSS was 99.1% for Low-Risk pts and 25.7% for High-Risk patients (HR 112.96; $p < 0.001$), capturing 4 out of 5 melanoma specific deaths in the CP-GEP High-Risk group. The final survival analysis of the whole cohort will be presented at the congress. **Conclusions:** This study shows that CP-GEP has the potential to stratify pts with early-stage melanoma who did not undergo SLNB based on their risk of recurrence. Pts with CP-GEP Low-Risk have a good long-term survival. Contrary, pts with CP-GEP High-Risk have a high risk of recurrence. CP-GEP may have the potential to stratify pts beyond SLNB. 1. Amaral et al, ASCO 2022. 2. Amaral et al, EJC 2023. Research Sponsor: None.

9576 Poster Session

Antigen-specific profiling for neoadjuvant anti-PD-1 therapy in melanoma.

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Background: Anti-PD-1 therapy (aPD-1) has had significant clinical success in extending survivability of melanoma patients. However, two-third of the patients do not achieve long-lasting benefits, and currently, there exists no reliable method for predicting clinical response. We test whether monitoring melanoma-specific CD8 T cells in blood, lymph node, and tumor enables us to gain insights into the mechanism of clinical resistance, and identify potential predictive biomarkers. **Methods:** We leveraged a phase 2 clinical trial of neoadjuvant PD-1 blockade at University of Pennsylvania where patients with stage III melanoma patients receive a pre-treatment biopsy, treatment with a single dose of the aPD-1 therapy, followed by tumor and lymph node resection 4 weeks later, allowing for access to paired blood and tumor samples. We used a combinatorial tetramer system to track panels of 10 HLA-restricted melanoma and viral-specific CD8 T cell populations simultaneously. **Results:** Out of 35 patients analyzed, 53% of patients had detectable melanoma-specific CD8 T cells. Notably, these cells exhibited exhausted phenotypes both in blood and tumor, whereas viral-specific T cells displayed features resembling effector and memory CD8 T cells in blood and tumor, respectively. Thus. the presence of tumor antigen emerges as a crucial determinant in shaping the phenotype of melanoma-specific CD8 T cells, above that of the tissue microenvironment. Analysis of resected lymph node samples following PD-1 blockade reveals their supportive role in activating and proliferating anti-tumor T cells. Finally, pathologic responders to PD-1 blockade are characterized by both a higher quantity and a less exhausted phenotype of tumor-specific CD8 T cells. This suggests that assessing both the quantity and quality of these T cells can serve as a predictive indicator to distinguish responders from non-responders. **Conclusions:** These findings highlight the feasibility of antigen-specific profiling in a clinical trial setting, the importance of melanoma-specific CD8 T cells in checkpoint blockade responses, and their potential use an early on-treatment biomarker of clinical outcomes. Research Sponsor: U.S. National Institutes of Health; K08 CA230157; Parker Institute for Cancer Immunotherapy; Tara Miller Foundation; U.S. National Institutes of Health; R01 CA273018; U.S. National Institutes of Health; P50 CA174523; U.S. National Institutes of Health; P30 CA016520; Damon Runyon Clinical Investigator Award; Doris Duke Clinical Scientist Development Award; W.W. Smith Charitable Trust Award; Institute for Translational Medicine and Therapeutics of the Perelman School of Medicine; Pew-Stewart Stewart Scholars Program in Cancer Research.

9577 Poster Session

Use of early circulating tumour DNA dynamics in patients with stage III melanoma receiving neoadjuvant combination immunotherapy.

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Background: Neoadjuvant therapy in resectable stage III cutaneous melanoma improves relapse-free survival compared to adjuvant therapy alone and is now a standard of care.While pathological response can help predict recurrence risk and the need for further treatment, more biomarkers are required. We investigated circulating tumour DNA (ctDNA) as a predictive biomarker for recurrence in stage IIIB/C melanoma patients following neoadjuvant immunotherapy and surgery. **Methods:** We retrospectively analysed plasma samples collected at baseline and six weeks post-surgery from 30 patients enrolled in the OpACIN-neo and PRADO clinical trials, who received two cycles of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) before surgery. Cell free DNA (cfDNA) underwent pre-amplification followed by tumour-informed mutation detection analysis using droplet digital polymerase chain reaction (ddPCR) with the Bio-Rad QX600 PCR system. BRAF mutations were identified in 60% of patients through tumour tissue sequencing. Following neoadjuvant therapy, 7/30 (23%) achieved complete pathological response (pCR), 5/30 (17%) near pCR, 4/30 (13%) partial response, and 14/30 (47%) non-response (pNR). **Results:** Baseline ctDNA was detectable in 15/30 (50%) patients using the pre-amplification ddPCR method. At median follow-up of 47 months, 9/30 (30%) patients recurred, with a median time to recurrence of 8 months (range 6 to 29 months). Post-surgery, ctDNA was detectable in 4/9 patients who recurred; all four were pathological non-responders and recurred with distant, unresectable disease. Among the 15 ctDNA-positive patients at baseline, 13/15 (87%) patients achieved ctDNA clearance while 2/15 (13%) remained persistently ctDNA-positive; with a subsequent relapse rate of 0% and 100% respectively. ctDNA detection post-surgery predicted patients at higher risk of disease recurrence [relapse-free survival (RFS) hazard ratio (HR) 7.83, 95%CI 0.82-74.48; p=0.0002] and poorer melanoma-specific survival (MSS) [HR 6.35, 95% CI 0.36-110.70; p=0.0337]. **Conclusions:** Post-surgery ctDNA positivity can signal imminent recurrence, thus offering a window for personalised adjuvant therapy modification. Research Sponsor: None.

9578 Poster Session

Neoadjuvant immune checkpoint inhibitors for patients with resectable stage III/IV melanoma: A nationwide real-life study in France (NEOMEL).

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Background: Several studies have shown the efficacy of neoadjuvant treatment (NT) with immune checkpoint inhibitors (ICI) for resectable stage III/IV melanoma. However, real-life data are lacking. **Methods:** NEOMEL is a national multicenter retrospective study assessing the efficacy and tolerability of NT with ICI (NT-ICI) for resectable metastatic melanoma in a real-life setting. Data were obtained in patients (pts) with resectable stage III/IV melanoma who initiated NT-ICI (at least one infusion). Primary endpoint was pathologic complete response (pCR) (i.e no residual tumor) rate. Secondary endpoints were pathologic response (pR) according to INMC, radiologic response (RECIST), safety profile (CTCAE) and survival outcomes. **Results:** A total of 166 pts with resectable stage III/IV melanoma were included. Median age was 67 years (range, 24-96). Most pts had primary cutaneous melanoma (n=157, 89%), stage IIIB-D disease (n=156, 94%); a BRAF V600-mutant melanoma was observed in 47% (n=78); 8% (n=14) pts had received a previous systemic treatment. The median number of infusions of NT-ICI was 3 (range, 1-5). ICI regimens were anti-PD-1 monotherapy (n=122, 73%) or nivolumab + ipilimumab (NIVO + IPI) (n=44, 27%). Median follow-up was 6.5 months (range, 1-85). Overall, 143 pts (86%) underwent surgery. A pCR was observed in 44% of pts (n=63/143), including 52% (n=51/99) treated with anti-PD-1 monotherapy, and 27% (n=12/44) treated with NIVO + IPI. Of note, 78 pts (54%) were treated with 3 infusions of pembrolizumab (PBZ) (according to SWOG 1801 protocol) and had a pCR in 45% (n=35). A pR was assessed according to INMC criteria in 58% of pts (n=83/143): 51% of pCR (n=42), 8% of near-pCR (n=7) corresponding to a major pR of 59% (n=49/83), 16% of pathologic partial response (n=13) and 25% of pathologic non-response (n=21). Twenty-three pts (14%) did not undergo surgery because of progressive disease (n=10), clinical and radiologic responses (8 complete responses, 1 partial response, 1 stable disease), toxicity (n=2) or patient's choice (n=1). Radiologic overall response rate according to RECIST (data available after NT in 49% of pts) was 54% (n = 44/82). All grade immune-related adverse events (irAEs) of NT-ICI occurred in 31% (n=51) of pts, including grade 3-4 irAEs in 10% (n=17) and one grade 5 irAE (pneumonitis with PBZ). Severe irAEs (grade 3 or more) were observed in 4% (n=4/99) of pts treated with anti-PD1 monotherapy and 32% (n=14/44) of pts treated with NIVO + IPI. Adjuvant treatment was started for 120 pts (84%). At last follow-up, 26 pts (18%) have had recurrence after surgery, including 3 pts with a pCR and 23 pts with a non-pCR to NT-ICI. Survival data are not yet available. **Conclusions:** NT-ICI for advanced melanoma demonstrated its efficacy with high rates of pCR in a real-life setting and an acceptable safety profile, particularly NT anti-PD1 monotherapy. Research Sponsor: None.

9579 Poster Session

Neoadjuvant immunotherapy (neoIT) in melanoma: A prediction tool for pathological response and recurrence, and the role of adjuvant (Adj) therapy (Tx) to improve recurrence-free survival (RFS).

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Background: NeoIT with anti-PD-1 (PD1) showed better event-free survival than adjuvant (adj) IT and is standard of care for pts with stage IIIB–D melanoma. Many pts achieve a Major Pathological Response with neoIT (MPR; complete [pCR] or near-complete [near-pCR] pathological response) and may not require additional Tx; pts with non-MPR (partial [pPR] or no [pNR] pathological response) are at higher risk of recurrence, and may benefit from adj Tx. We sought to: 1) predict pts with non-MPR and at higher risk of recurrence with PD1-based neoIT, and 2) study the role of adjuvant (adj) Tx in pts with pNR. **Methods:** Pts with stage IIIB–D melanoma treated with PD1-based neoIT were included. Demographics, disease characteristics, baseline blood parameters, radiological response, and clinical outcomes were examined. A multivariate penalized logistic regression model was developed to predict non-MPR and recurrence. **Results:** Of 184 pts, 30 (16%) had PD1 alone, 107 (58%) had PD1 + anti-CTLA-4 (PD1+IPI), and 47 (26%) had PD1 + novel IT agents. Of the 179 (97%) who underwent surgery, 114 (64%) had MPR (95 [53%] with pCR and 19 [11%] with near-pCR) and 65 (36%) had non-MPR (20 [11%] with pPR and 45 [25%] with pNR). Five pts did not receive surgery (due to clinical progression in 4). The combination of pre-neoIT clinical and pathological features predicted non-MPR pts with an AUC of 0.73. The addition of radiological response (% change from baseline in tumor size: adjusted odds ratio [AOR] 18.94, p=0.0001) to clinical features (pre-neoIT neutrophil [AOR 1.29, p=0.0476] and lymphocyte count [AOR 1.64, p=0.0467], largest lymph node long axis [AOR 1.02, p=0.1056], hemoglobin level [AOR 0.99, p=0.6728], and primary tumor staging [T4 vs. T1; AOR 1.83, p=0.0457]) improved the predictive accuracy (AUC = 0.86). For pts with ≥6 months FU, 2% (2/98) of pts with MPR and 34% (20/58) of pts with non-MPR (20% [4/20] with pPRs and 42% [16/38] with pNR) recurred. Amongst non-MPR pts, the combination of mitotic rate in the primary melanoma (>1 vs. ≤1 mitosis/mm^2; AOR 8.23, p<0.0001) and % change from baseline in tumor size (AOR 13.59, p=0.0005) predicted recurrence with an AUC of 0.81. The median % change from baseline in tumor size was +12% in recurrent vs -11% in non-recurrent pts (p=0.0047). Pts with >30% reduction in tumor size did not recur. Of the 38 pts with pNR, the recurrence rate was 64% (7/11) with no adj Tx, 27% (3/11) with adj targeted therapy (TT), and 38% (6/16) with adj PD1. **Conclusions:** Clinical, pathological, and radiological features can accurately predict MPR or non-MPR to neoIT, as well as recurrence, facilitating response-directed Tx. Acknowledging the small numbers of patients, these early data suggests that Adj TT or PD1 reduces recurrence and should be discussed with pts with pNR. De-escalation of surgery (± adj Tx) should be investigated in MPR pts. Research Sponsor: None.

9580 Poster Session

Neoadjuvant pembrolizumab and lenvatinib in resectable mucosal melanoma: NeoPlus study update.

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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, 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 Relapse free survival (RFS, time from surgery to any event), Overall survival (OS) and safety. **Results:** Between Sep 2021 and Apr 2023, 26 pts were enrolled, median age was 57 yrs(range: 49-75), 19 were female. Primary sites included: 11 female genital, 8 ano-rectal, 5 head & neck (1 nasal, 4 oral),2 esophageal. 15 pts (58%) were localized disease,11 (42%) were regional lymphatic disease. BRAF V600, NRAS or KIT mutations were presented in 1, 3 and 2 pts, respectively. 21 pts underwent surgery, 2 pts had a pCR (9.5%), 2 near PCR, 4 pPR, with a pathologic response rate of 38% (8/21,95%CI 18-62%). 5 pts did not proceed with planned surgery for pts preference. As of Dec 2023, 12 of 21 resected pts had relapsed (9/11 in female genital,2/4 in ano-rectal, 1/5 in head & neck). Median follow up time was 19.1 months (95%CI 13.7-24.5). Median RFS was 12.4 months (95%CI 4.0-20.8), no difference was observed among these primary sites (female genital: 6.6 months, ano-rectal: 14.1 months, head & neck: not reached). Median DMFS was not reached. IHC data of the resected tumor showed higher CD8+ T cells density in responders (R: pCR+near PCR+ pPR) than non-responders (NR: pNR) ($p = 0.046$). Tertiary lymphoid structures were detected in 9 pts. Most common TRAEs were hypertension (13, 50%), proteinuria (12, 46%), LDH increased (9,35%), hypothyroidism (8, 31%). Three pts experienced a dose reduction and 5 experienced a dose interruption due to an AE. No grade 4-5 toxicities were observed. **Conclusions:** Updated results confirmed that the combination of pembrolizumab plus lenvatinib as neoadjuvant therapy had moderate anti-tumor efficacy in resectable mucosal melanoma. Increased CD8+ T cell infiltration was observed in tumor with pathologic response, supporting further investigation in mucosal melanoma. Research Sponsor: None.

9581 Poster Session

Incidence and risk factors for central nervous system (CNS) metastasis (met) in patients (pts) with stage III melanoma treated with adjuvant (ADJ) anti-PD1 immunotherapy (IMT).

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Background: The identification of risk factors for CNS met in stage III melanoma pts will facilitate the development of personalized surveillance strategies. Previously we characterized the incidence (3.6%, 9.6%, and 15.8% at 1, 2, and 5 yrs) and risk factors for CNS met in pts diagnosed with stage III melanoma from 1998 to 2014. It is unknown if the incidence of CNS met has changed in the ADJ IMT era. **Methods:** We performed an institutionally approved retrospective chart review of pts diagnosed with stage III melanoma treated with ADJ IMT between 1/1/2018 and 12/31/2020 at MD Anderson Cancer Center (MDA) or the Melanoma Institute of Australia (MIA). Exclusion criteria included mucosal or uveal melanoma or prior systemic therapy (other than ADJ interferon). Pts had to have CNS imaging within 1 month before or 4 months after stage III diagnosis. Pt and tumor features, treatments, and distant recurrence events (CNS met; non-CNS met) were captured. Time-to-CNS and time-to-non-CNS met were computed from start date of ADJ IMT to date of CNS/non-CNS met. Cumulative incidence of distant met events was determined using competing risks (death) and pts alive with no met at last follow-up were censored. Associations were determined using proportional subdistribution hazards regression models; group differences were assessed using Gray's test. **Results:** 361 pts were included in the analysis (MDA, 212; MIA, 149). With a median FU of 34.1 months (range 1.7-61.9), 128 (35.5%) of pts were diagnosed with distant mets. Among pts with distant mets, 56 had CNS met (15.5% of full cohort; 43.8% of pts with distant met); 24 (18.8% of pts with distant mets) pts had CNS met at initial diagnosis of stage IV disease. The 1-, 2-, and 5-yr rates of CNS met in the full cohort were 7%, 12%, and 17%. There was no difference in CNS met incidence between MDA and MIA. On univariate analysis, risk of CNS met was associated with AJCC stage IIID (Hazard Ratio [HR] 6.4; 95% Confidence Interval [CI] 2.2 – 18.8, $p<0.001$); increased primary tumor Breslow thickness (HR 1.1, CI 1.1 – 1.2, $p<0.001$), ulceration (HR 2.8; CI 1.5 – 5.1, $p<0.001$), and mitotic rate > 9/mm (HR 2.3; CI 1.1 – 4.6, $p=0.025$). There was a trend for decreased risk of CNS met in pts that stopped ADJ IMT due to toxicity (HR 0.4; CI 0.2 – 1.1, $p=0.08$). Multivariable (MV) model with these features did not identify any significant ($p<0.05$) associations with CNS met. Primary tumor ulceration and mitotic rate were significantly associated with non-CNS met on MV analysis. **Conclusions:** Despite the established impact of ADJ IMT on distant met free survival, the incidence of CNS met in stage III melanoma pts treated with ADJ IMT remains high. The results support the need for continued investigation of risk factors, prevention strategies and optimal surveillance for CNS met in stage III melanoma pts. Research Sponsor: American Cancer Society; Melanoma Research Alliance; National Cancer Institute/U.S. National Institutes of Health; 5P50CA221703-05.

9582 Poster Session

Prognosis of deep margin excisions within or beyond subcutaneous fat for invasive acral melanoma of the sole: A multi-institutional retrospective study.

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Background: There is scant evidence concerning the optimal deep margins for wide excision (WE) of primary tumors in melanoma surgery. Despite the importance of preserving plantar subcutaneous fat in the sole for cushioning function, no study data exists on the optimal depth margins for acral melanoma of the sole (sole AM). Thus, we aimed to compare the prognosis associated with different deep margin excisions for sole AM. **Methods:** We conducted a retrospective review of clinical records from patients with invasive resectable sole AM who underwent WE of the primary tumor across 41 Japanese institutions. The prognosis was compared between two groups based on different deep margin excisions: those with tumors excised within (S-group) or beyond (D-group) the subcutaneous fat. Kaplan—Meier analysis and multivariable Cox proportional hazard models were used to estimate the survival probabilities. Propensity-score matching (PSM) was used to adjust for numerical differences in baseline characteristics. **Results:** This study included a total of 425 patients (median age 73 years) with invasive sole AM, who underwent WE based on the peripheral surgical margins recommended in the National Comprehensive Cancer Network guidelines. The median follow-up period was 48 months. The S-group included 263 patients and the D-group 162 patients. The baseline characteristics significantly differed between the two groups in terms of Breslow thickness ($P < 0.01$), presence of ulcer ($P < 0.01$), and presence of in-transit, satellite, and regional lymph node metastasis ($P < 0.01$). The other baseline characteristics were similar. Although local recurrence-free survival (LRFS) did not significantly differ between groups, the S-group showed significantly longer disease-free (DFS) and overall survival (OS) than the D-group (5-year LRFS, 96% vs. 90%; $P = 0.08$; 5-year DFS, 70% vs. 41%; $P < 0.01$; 5-year OS, 84% vs. 69%; $P < 0.01$). In contrast, multivariable Cox proportional hazard models showed no significant differences in LRFS, DFS, and OS between the two groups (LRFS, hazard ratio [HR], 1.87, $P = 0.18$; DFS, HR, 1.05, $P = 0.77$; OS, HR, 1.08, $P = 0.72$). After PSM, the groups were balanced at a 1:1 ratio (128 patients in each group) and no statistical significance was found in LRFS, DFS, or OS between the adjusted groups (5-year LRFS, 97 % vs. 91 %; $P = 0.40$; 5-year DFS, 65 % vs. 48 %; $P = 0.053$; 5-year OS, 80 % vs. 73%; $P = 0.18$). Subgroup analysis of stage I, II, and III also indicated no statistical significance in LRFS, DFS, and OS between the two groups (stage I: LRFS, $P = 0.11$; DFS, $P = 0.65$; OS, $P = 0.26$; stage II: LRFS, $P = 0.37$; DFS, $P = 0.06$; OS, $P = 0.85$; stage III: LRFS, $P = 0.29$; DFS, $P = 0.67$; OS, $P = 0.85$). **Conclusions:** In sole AM, WE with excessive deep margins beyond the subcutaneous fat did not improve prognosis. Excision of the primary tumor within the subcutaneous fat may be an optimal deep margin for sole AM. Research Sponsor: The Japanese Society for Dermatologic Surgery Award for Encouragement of Academic Research.

9583 Poster Session

Identifying the high risk group in stage pT1bN0 cutaneous melanoma.

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Background: In recent years, there has been a substantial improvement in prognosis for patients diagnosed with stage II or III melanoma due to the advent of adjuvant and neoadjuvant therapy. At the same time, significant percentage of melanoma deaths are caused by prevalent cases of thin melanoma. In this work, we aimed to identify the stage pT1bN0 melanoma subgroup with the worst prognosis. **Methods:** All cases of stage pT1b melanoma (with negative sentinel node biopsy) treated between 1998 and 2022 in high-throughput reference center were analyzed. Patients were followed for ten years or up to lost to follow-up or death. Patients alive at 10 year mark were censored. The patients were divided into groups with BOTH pT1b features (i.e., Breslow thickness $>$ 0.8mm AND ulceration) vs those with just ONE of those features. Additionally, patients' sex, the tumor's pathological subtype, and mitotic index were analyzed. The Kaplan-Meier and the Cox proportional model were used in statistical analysis. **Results:** There were 665 cases identified. 63% of patients were female, median age was 49 (IQR: 38-60). 70% of patients were classified as pT1b due to Breslow thickness, 21% due to ulceration and 9% due to BOTH features. 48% of patients had superficially spreading melanoma, 3% - acral, 9% - nodular while other patients had other/unspecified subtype. The median mitotic index was 1/mm2, but this feature was missing in 46% of cases. Overall, 61 patients died during the follow-up. The 10-year overall survival (OS) rate for the whole group was 86% (95% CI: 83-90%). In a multivariable model, patients with BOTH IB features (HR 2.1, 95%CI:1.1-4.2), nodular or acral melanoma (HR 2.2, 95%CI:1.2-4.1) and males (HR 2.6, 95%CI:1.6-4.4) had worse prognosis; the mitotic index was not predictive for OS in this model. In patients with BOTH pT1b features the 10 year survival rate was 75% (95%CI: 62-89) and 87% (95%CI: 84-91%) in case of just one feature (log-rank p=0.008). **Conclusions:** There is a specific subgroup of patients diagnosed with stage IB who have a relatively bad prognosis. Focusing on perioperative treatment or on a more strict follow-up schedule in this group may prove beneficial. Research Sponsor: None.

LBA9584 **Poster Session**

Quality of life with neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) versus adjuvant nivolumab in resectable stage III melanoma: 36-week data from the phase 3 NADINA trial.

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9585 Poster Session

Primary immunotherapy monotherapy (PRIMO) in locally advanced cutaneous squamous cell carcinoma.

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Background: Neoadjuvant immunotherapy is a potential curative approach to patients with locally advanced cutaneous squamous cell carcinoma (cSCC) that offers an attractive alternative to traditional, often morbid surgery and/or radiation. In this study, we report our initial institutional experience treating patients with primary immunotherapy monotherapy (PRIMO) and reserving surgery or radiation for progression only. **Methods:** Patients with primary or recurrent locally advanced cSCC (AJCC 8 T3-4 or node positive or in-transit metastases) in whom surgical resection and/or definitive radiation were deemed excessively morbid or futile and were treated with PRIMO were included in an IRB-approved database. Patients were treated with IV cemiplimab (350mg q 3week) or pembrolizumab (200mg q3week or 400 q6week). Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) was scored according to iRECIST criteria. Kaplan Meier analysis was used to estimate overall survival (OS) and progression free survival (PFS). Univariate analysis (UVA) for PD was performed using Chi square for categorical variables and Kruskal-Wallis for continuous variables. **Results:** This study included 36 patients treated between 2017-2023, with a median age of 80 (61-96), and a median follow up of 13.5 months (8-20.5). Most patients had lesions on the head and neck (32; 88.9%), recurrent disease (26; 72.2%), and T3/4N0 disease (20; 55.6%), while 18 patients (50.0%) had nodal disease or in-transit metastases. Cemiplimab was used in 31 patients (86.1%) while pembrolizumab was used for 5 patients (13.9%). Twelve patients (33.3%) stopped PRIMO due to an immune-related adverse event (irAE). 1 and 2yr OS and 1 and 2yr PFS were 76%, 64%, 72% and 51%, respectively. Best initial response to PRIMO was a CR in 15 (41.7%), PR in 14 (38.9%), SD in 3 (8.3%) and PD in 4 (11.1%) patients. All 3 lesions (100%) with SD and 3/14 lesions (21.4%) with PR ultimately progressed with a median duration of response of only 3 months (2.0-6.8), while all 15 lesions (100%) with a CR and 11/14 lesions with a PR (78.5%) remain controlled at last follow up with a median duration of response of 15.5 months (8.8 – 23.3) ($p<0.001$). The median duration of months of ongoing response after the completion of PRIMO was 11 (0-57). The median number of treatment cycles was 14 (2-36) in all patients, and 16 (2-36) in the 26 patients that did not progress. The only variable significantly associated with PD on UVA was the lack of irAE; 10/26 (38.5%) patients who did not have an irAE experienced PD, while 0/12 patients (0%) who had an irAE experienced PD ($p=0.035$). **Conclusions:** The use of PRIMO for locally advanced cSCC produces impressive response rates that appear durable without any additional therapy. This attractive alternative to the emerging neoadjuvant paradigm deserves prospective validation with longer term follow up. Research Sponsor: None.

Characterization of driver oncogenic mutations of in-transit melanoma metastases.

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Background: In-transit melanoma (ITM) is a distinctive form of melanoma metastasis, marked by aggressive locoregional progression and characterized by the entrapment of tumor cells within the lymphatic channels before reaching regional lymph nodes (LN). The mechanisms leading to lymphatic trapping rather than progression to distant metastasis are not well-understood. Previous research indicates a clonal origin for ITM, suggesting specific early-stage genetic alterations may drive this clinical phenotype. In this study, we sought to identify driver oncogenic mutations specific to ITM that may serve as potential targets. **Methods:** We analyzed data from the MSK-IMPACT database, which includes targeted sequencing of 341-468 genes for patients with cutaneous melanoma. Patients were stratified into four groups based on the type of sample sequenced: in-transit, primary tumor, regional LN, and distant metastases. We examined the prevalence of driver mutations and genetic variants across these groups, adjusting for multiple comparisons. **Results:** A total of 528 patients were included, of which 74 were in the ITM, 103 in the primary, 133 in the regional LN, and 218 in the metastatic group. The mean age of the cohort was 59 years (SD = 16) and 67% were male. Among the in-transit samples, 68% were treatment-naïve at the time of sequencing, 36% received anti-PD1 monotherapy, and 12% received anti-PD-1 combination therapy. None of the patients received targeted therapy. NRAS Q61 driver mutations were significantly more common in ITM than all other groups (all $p<0.05$). NF-1 driver mutations were significantly less common in ITM than distant metastasis ($p=0.007$) (Table). Comparative analysis across all genes showed a lower incidence of NF-1 mutations in ITM relative to metastatic samples (12% vs 38%, $p=0.007$). Gene interaction analysis showed mutual exclusivity between NRAS and PAK5 mutations in ITM ($p=0.02$), but not in other groups ($p>0.05$). **Conclusions:** This study reveals distinct driver oncogenic mutations specific to ITM, characterized by a high incidence of NRAS mutations, retained NF-1 function and the novel finding of mutual exclusivity between NRAS and PAK5. Closer examination of the interplay between NRAS, NF-1 and PAK5 interactions in ITM may provide deeper insights into the molecular mechanisms of ITM and offer potential therapeutic targets for ITM. Research Sponsor: None.

Difference in driver class mutation between in-transit, primary, regional lymph node, and metastatic melanoma samples.

	In-Transit (n=74)	Primary Tumors (n=103)	Regional Lymph node (n=133)	Distant Metastases (n=218)	p-value
V600E BRAF	16 (22%)	29 (28%)	39 (29%)	45 (21%)	0.37
Non-V600E Class I BRAF	3 (4%)	9 (9%)	8 (6%)	13 (6%)	0.75
Class II/III BRAF	5 (7%)	5 (5%)	14 (11%)	11 (5%)	0.37
NRAS Q61	32 (43%)	22 (21%)	33 (25%)	51 (23%)	**0.014***
NF-1	7 (10%)	22 (21%)	22 (17%)	69 (32%)	**0.007***
KIT/PDGFRA	1 (1%)	4 (4%)	3 (2%)	4 (2%)	0.64
Other	10 (14%)	12 (12%)	14 (11%)	25 (12%)	0.94

9587 Poster Session

Biomarker analysis and updated clinical outcomes: Neoadjuvant systemic treatment (NST) with nivolumab (nivo) and relatlimab (rela) in surgically resectable melanoma.

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Background: NST with immune checkpoint blockade (ICB) improves clinical outcomes over upfront surgery followed by adjuvant treatment (tx) in patients (pts) with stage III, surgically resectable melanoma. The NST platform also provides an opportunity for deep translational analysis to identify baseline (BL) biomarkers predicting pathologic response and to gain insights into resistance. BL biomarkers, including gene expression signatures (GES) such as IFN-γ/ tumor mutational burden, tumor infiltrating lymphocytes, and presence of tertiary lymphoid structures, have been associated with pathologic response to NST with anti-PD1 and/ or anti-CTLA4 antibodies. These studies have not evaluated the newest ICB combination, nivo (anti-PD1) + rela (anti-LAG3), which achieved a major pathologic response rate (MPR) (≤10% viable tumor) of 63% in a Ph II study (NCT02519322). Here we report GES analysis from BL and longitudinal tumor tissues obtained on this study and correlations with outcomes. **Methods:** Longitudinal tissue was collected from 30 pts treated on the clinical trial and available RNA analyzed using the NanoString nCounter PanCancer IO360 panel. Clinical outcomes, including recurrence and event-free survival, were also updated with longer follow-up. Pts were grouped into MPR and non- major pathologic responders (non MPR). Normalization, differential expression / GES evaluation was performed using nSolver Advanced Analysis software. Differential expression is fit on a per signatures basis using a linear model for analysis. P-values were adjusted within each analysis and on the grouping variable level difference t-test using the Benjamini and Yekutieli False Discovery Rate adjustment to account for correlations amongst the tests. BL analysis was grouped based on pathologic response, MPR vs non-MPR. **Results:** Of the 30 pts (median follow up 44 months), 53 RNA samples from 26 patients (9 NR and 17 R) were included in the full analysis. Immune GES with significantly higher (adjusted $p < 0.05$) differences at BL in MPR vs non-MPR included: B cells, CD45, CD-8+ T cells, TIGIT, IDO1, and IFN-γ. Significantly higher B7-H3 GES at BL was associated with non MPR. Additional analyses (i.e., cell population changes over time) and association with event outcomes are underway. **Conclusions:** To our knowledge, this is the first longitudinal RNA analysis reported from pts treated with nivo+rela. BL immune features associated with major pathologic response include higher GES of B cells, CD45+ cells, CD8 T cells, and increased expression of TIGIT, IDO and IFN-γ. Additionally, higher B7-H3 in non MPR pts may indicate a clinically actionable strategy for further evaluation. Ongoing analyses of longitudinal samples and correlations with clinical outcomes are underway and will be presented. Clinical trial information: NCT02519322. Research Sponsor: BMS.

9588 Poster Session

Serum multiplex analysis of checkpoint proteins in association with immune-related adverse events in patients with melanoma receiving adjuvant anti-PD-1 therapy.

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Background: Immune checkpoint inhibitors have significantly improved melanoma (MEL) patient (PT) outcomes. Immune-related adverse events (irAEs) may cause significant morbidity, rarely including death. Soluble immune checkpoints have been identified as biomarkers of autoimmune activity and potential off-target pathology. Understanding their relationship to pathologic outcomes may assist in the identification of PTs at highest risk of irAEs. **Methods:** PTs with resectable stage IIB-IV MEL who received adjuvant anti-programmed-death-1 (PD-1) therapy were identified from the University of Pittsburgh's MEL Center biospecimen repository (N=273). MILLIPLEX Human Immuno-Oncology Checkpoint Protein Panel 2 was used to study serum levels of immunomodulatory proteins. Mean pretreatment serum levels in PTs with and without irAEs were compared using a two-sample t-test after performing Box-Cox transformation for non-normally distributed data. **Results:** Sera from 43 PTs were analyzed. The cohort included 28 (65.1%) male, mean age at diagnosis (62), including MEL stage IIIA = 7 (16.3%), IIIB = 16(37.2%) and IIIC = 20(46.5%). The most common irAEs (n=24, 55.8%) were thyroiditis (n=9, 20.9%), dermatitis (n=8, 18.6%), and adrenal insufficiency (n=9, 21.0%). Multiple irAEs were observed amongst 22 (51.2%) PTs with $\geq$3 irAEs and 6 (13.9%) with 5 irAEs. Visceral irAEs included Hepatitis (n=3, 7.0%), pneumonitis (n=2, 4.7%), and colitis (n=5, 11.6%). Seven of 8 patients with visceral irAEs required corticosteroids. Siglec-7 (mean 23.4 vs 3.51 pg/mL, p=0.018) and siglec-9 (mean 77.0 vs 33.1 pg/mL, p=0.049) were significantly elevated in the PTs who developed any irAE. After stratifying for each individual irAE, PTs with thyroiditis had elevated Nectin-4 (mean 2785.5 vs 494.7 pg/mL, p$<$0.001) and serum arginase (mean 2437.5 vs 1383.1 pg/mL, p= 0.046) was elevated in PTs who developed colitis. PTs with hepatitis demonstrated increased galectin-3 (mean 10103.9 vs 9915.3 pg/mL, p=0.045) and decreased levels of CD40L (mean 2869.2 vs 9496.9 pg/mL, p=0.033). In PTs with dermatitis B7-H3 (mean 2503.3 vs 732.4 pg/mL, p=0.009) and MHC class I polypeptide-related sequence B (mean 1598.0 vs 259.1 pg/mL, p=0.048) were elevated. **Conclusions:** We have demonstrated unique serum checkpoint protein profiles related to specific irAEs in melanoma patients receiving adjuvant anti-PD1. Further studies are warranted to confirm and validate the utility of these irAE predictors during adjuvant anti-PD-1. Research Sponsor: None.

9589 Poster Session

Metabolic factors affecting response to adjuvant anti-PD1 therapy for melanoma.

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Background: Given the intersection between metabolism and the immune system, and with the increasing use of immune checkpoint inhibitors (ICIs) in the treatment of solid tumors, it is important to determine whether metabolic factors are associated with outcomes for patients treated with ICIs. Obesity is often associated with improved response to immunotherapy for patients with melanoma. However, the impact of other metabolic disorders, such as type 2 diabetes (T2DM), hypertension (HTN), and hyperlipidemia (HLD), on immunotherapy response is not as well understood. The purpose of this study is to determine the impact of these metabolic disorders on immunotherapy treatment. **Methods:** Patients with stage II or III melanoma who were treated with adjuvant anti-PD-1 therapy and consented to the University of Pittsburgh Melanoma Center repository were included in this study. A retrospective chart review was conducted of the eligible 281 patients. **Results:** HTN, T2DM, HLD, and body mass index (BMI) $>$ 35 were analyzed together in two multivariate Cox proportional hazard models, one considering overall survival (OS) and the other recurrence free survival (RFS). T2DM (n=49) was significantly associated with both a decreased OS (HR=2.51, 95% CI 1.14-5.52; p=0.0219) and RFS (HR=1.92, 95% CI 1.16-3.164; p=0.011). No significant differences were observed for patients with HTN (n=156) in OS (HR=1.45, 95% CI 0.73-2.87; p=0.29) or RFS (HR=1.22, 95% CI 0.80-1.86; p=0.35), HLD (n=140) in OS (HR=0.62, 95% CI 0.30-1.29; p=0.20) or RFS (HR=0.69, 95% CI 0.44-1.07; p=0.098), or BMI $>$ 35 in OS (HR=1.01, 95% CI 0.48-2.13; p=0.99) or RFS (HR=0.78, 95% CI 0.47-1.29; p=0.34). After adjusting for common pre-treatment comorbidities (coronary artery disease, chronic kidney disease, and smoking), age, and sex, T2DM was no longer significantly associated with reduced OS (HR=1.78, 95% CI 0.83-3.8; p=0.14), but the association with RFS remained significant (HR=1.69, 95% CI 1.04-2.76; p=0.034). In patients with T2DM alone, metformin use (n=24) during immunotherapy treatment was associated with improved OS in univariate (HR=0.28, 95% CI 0.08-0.9; p=0.0385) and multivariate (HR=0.18, 95% CI 0.05-0.7; p=0.0098) analyses controlling for age, sex, and the comorbidities listed above. It was also near significant for increased RFS in a univariate (HR=0.46, 95% CI 0.20-1.06; p=0.067) and multivariate (HR=0.42, 95% CI 0.17-1.06; p=0.065) model. Baseline A1C (n=15) values were not significantly associated with OS (HR=0.18, 95% CI 0.001-24.7; p=0.49) or RFS (HR=0.60, 95% CI 0.21-1.76; p=0.35) in univariate models. **Conclusions:** T2DM is associated with decreased RFS for patients with melanoma treated with adjuvant anti-PD-1 therapy. Within the T2DM cohort, metformin use was associated with significantly improved RFS and OS. A1C did not correlate with either OS or RFS, suggesting that the effects of both T2DM and metformin may be independent of glycemic control. Research Sponsor: None.

9590 Poster Session

Combined EORTC FDG-PET/CT and RECIST 1.1 response criteria and prediction of pathological response to neoadjuvant nivolumab and ipilimumab for clinical stage III melanoma.

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Background: Accurate identification of pathological response to neoadjuvant therapy for clinical stage III melanoma before surgery may allow us to better tailor the treatment. RECIST 1.1 has shown poor concordance rates with pathological responses and EORTC FDG-PET/CT response criteria using SUV max is susceptible to internal and external variables leading to difficulty in determining accuracy appropriately. **Methods:** We conducted a multicenter retrospective analysis of patients with clinical stage III melanoma treated with neoadjuvant nivolumab 3mg/kg + ipilimumab 1mg/kg(N3+I1) for two cycles who did baseline and preoperative 18F-FDG-PET/CT. RECIST 1.1 and EORTC PETCT criteria were used to classify patients in terms of response. The pathological results were correlated to the image findings. **Results:** Between Jan 2019 and Jan 2024, 37 patients with clinical stage III melanoma treated with neoadjuvant N3+I1 were identified. Gender: 25 males (67%), median age (years): 58 (range: 31-78), BRAFV600 mut: 25(67%), positive nodes on baseline exam:1=30 (81%), 2=4(11%), and 3 or more =3(8%). Stage AJCC 8th edition: IIIB=23 (62%), IIIC=12 (32%), IIID=2(6%). Among them, 34 had baseline and post-neoadjuvant therapy PET-CT. Twenty-one (62%) had major pathological response (MPR) and 13(38%) had non-MPR. Using objective response and non-objective criteria to capture MPR and non-MPR, respectively, we found the following results: RECIST 1.1 (sensitivity= 48%, specificity=100%, accuracy=68%), EORTC-PET (sensitivity=90%, specificity=69%, accuracy=82%). Combining RECIST 1.1 and EORTC-PET/CT analysis, we found that: double objective responders (CR/PR and CMR/PMR, n=10) had 100% specificity to MPR and double progressors (PD/PMD, n=9) had 95% specificity to non-MPR. The only patient classified as double progressor that did not have non-MPR presented an intense inflammatory response with fever, pain and erythema leading to an increase in the size and number of lymph-nodes. No viable cells were found in the pathological report. **Conclusions:** Using combined RECIST 1.1 and EORTC-PET/CT response criteria may help to predict pathological response in patients with clinical stage III melanoma who undergo to neoadjuvant nivolumab and ipilimumab. Research Sponsor: None.

9591 Poster Session

Pathologic response rates to neoadjuvant pembrolizumab in locally advanced (LA) resectable cutaneous squamous cell carcinoma (cSCC).

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Background: Cutaneous squamous cell carcinoma (cSCC) is the second commonest cutaneous malignancy, accounting for 20% of cutaneous malignancies and 75% of non-melanoma skin cancer deaths. Anti-PD-1 is approved in unresectable and metastatic cSCC, and is associated with high rates of pathologic response in resectable locally advanced (LA) cSCC. We conducted a phase II single-arm neoadjuvant trial of pembrolizumab (P) in patients with PD-1 naïve resectable LA cSCC. **Methods:** Patients with AJCC/UICC ≥T3 (or T2 with ≥2 BWH high-risk features) and/or N+ disease were eligible. Patients received 2 cycles of P (200mg Q3W) prior to definitive surgery, and 15 cycles post-surgery (NCT04808999). The primary endpoint was pathologic complete response (pCR, defined as 0% residual viable tumor, RVT) per independent central pathology review. Key secondary endpoints included incidence of adverse events (AEs), recurrence-free survival (RFS), overall survival (OS), safety and unbiased spatial biomarkers. A selected panel of multiplex immunofluorescence imaging biomarkers were used by PredxBio Inc.'s computational pipeline to reveal spatial intratumor heterogeneity in the tumor microenvironment (TME). **Results:** Thirty patients were enrolled and received at least 1 cycle of P. The median age was 79 (59-93) years and patients were predominantly male (77%). One patient withdrew consent prior to surgery. Three patients died prior to definitive surgery: 2 from COVID-19, a third from a NSTEMI possibly related to P. Of the 26 response-evaluable patients, AJCC/UICC stage at baseline was high-risk T2, T3, N1, and N2 in 2 (8%), 12 (46%), 9 (34.5%), and 3 (11.5%) patients, respectively. We observed pCR in 15 (57%), pathologic partial response (pPR, 10% < %RVT <50%) in 2 (8%) and pathologic non-response (pNR, >50%RVT) in 8 (31%) patients. One patient is pending surgery. Postoperative radiotherapy (RT) was de-escalated in 54% of the patients (14/15 in pCR). Median RFS was 13 (pCR) versus 10.5 (non-pCR) months. One Grade 5 (NSTEMI) and two Grade 3 (hepatitis, colitis) treatment-related AEs were observed. Computational analysis identifies key spatial interactions between PDL-1+/CD68+ cells implicated in response to P. **Conclusions:** Neoadjuvant P is efficacious in resectable LA cSCC with a high pCR rate (57%). Three deaths were observed, including 2 unrelated to treatment and 1 possible Grade 5 cardiac irAE, reflecting the inherent risks of perioperative therapy in this patient population. RT was de-escalated in 93% of pCR patients. No relapse events in pCR patients. Spatial interactions between PDL-1+ cells and CD68+ macrophages have a role in therapeutic response and will be detailed along with other spatial analyses of the TME compartment that have an impact on outcomes. Clinical trial information: NCT04808999. Research Sponsor: None.

9592 Poster Session

Phase 1b trial of IFx-Hu2.0, a novel in situ cancer vaccine, in checkpoint inhibitor-resistant Merkel cell carcinoma (MCC) and cutaneous squamous cell carcinoma (cSCC).

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Background: MCC and cSCC have limited treatment options when refractory to immune checkpoint inhibitor (ICI) therapy. IFx-Hu2.0 (IFx) is a plasmid DNA encoding for an immunogenic bacterial protein, Emm55, formulated with a transfection agent for direct intratumoral (IT) injection. In this Phase 1b study, we evaluated the safety and efficacy of different schedules of IT IFx in patients (pts) with advanced MCC or cSCC. **Methods:** In the first trial stage (n=9), IT IFx was administered in up to 3 lesions on 3 schedules following a 3+3 exposure escalation schema; weekly x 1, 2, or 3. In the second trial expansion stage (n=11), IT IFx was administered weekly x 3. The primary objective of the study was to establish safety and feasibility of repeated IT administrations of the investigational agent. ≥80% completion of planned study therapy was predefined as a successful feasibility outcome. Given the proposed potential for immune priming effects of IFx, we performed an unplanned exploratory analysis of post-protocol treatment efficacy to evaluate response to ICI rechallenge. **Results:** We treated 22 pts (MCC, 13; cSCC, 9). All pts had received prior anti-PD(L)1 based treatment with disease progression being the reason for ICI discontinuation in all patients but one. Two pts did not complete planned study therapy due to rapid clinical progression and were replaced but included in the safety analysis. IT IFx was well tolerated at all dose schedules evaluated with 1 high-grade toxicity deemed possibly treatment related (G3 hepatitis in a patient recently treated with ICI). The study therefore met predefined study endpoints for safety and efficacy. After protocol specified IT therapy, 11 MCC pts and 6 cSCC pts were treated with anti-PD(L)1 based therapy as the immediate post-protocol treatment. Five of 9 (56%) evaluable MCC patients and 1 of 7 (14%) cSCC patients experienced an objective response to this ICI rechallenge, with duration of response ongoing in 4 patients (6+, 19+, 21+, 23+ months) and the two other responses lasting 23 and 33 months. The two remaining MCC patients were not evaluable for response from IO rechallenge due to radiation administered to the only measurable disease site(s), but both remain progression free at 11+ and 13+ months with previously progressive disease. **Conclusions:** IT IFx-Hu2.0 is safe and feasible to administer at weekly dosing repeated up to 3 weeks. An unplanned exploratory analysis revealed frequent (56%) and durable responses in advanced MCC to ICI re-challenge despite prior resistance to this class of drug, suggesting that IFx induced an immune priming effect. Preliminary biomarker analyses to investigate this phenomenon are ongoing and will be presented. Clinical trial information: NCT04160065. Research Sponsor: TuHURA Bioscience, Inc.

9593 Poster Session

The impact of adjuvant radiation therapy on disease-specific survival in stage I and II Merkel cell carcinoma: A SEER database analysis.

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Background: Merkel Cell Carcinoma (MCC) is a rare, cutaneous neuroendocrine tumor associated with poor prognosis. Adjuvant radiation therapy (RT) is commonly used for the treatment of locoregional disease, but the impact on survival remains controversial. Previous studies from the Survival, Epidemiology, and End Results (SEER) database have shown an overall survival benefit to adjuvant RT without controlling for important prognostic differences in comparison groups such as age. To better control for these variables, we examined the impact of postoperative adjuvant radiation therapy on stage I and II disease-specific survival using the SEER database. **Methods:** SEERStat was used to obtain and analyze the outcomes of 2423 histologically confirmed MCC patients treated with surgery monotherapy or surgery with postoperative radiation therapy between 2004 and 2020 in the 17-registry (November 2021) SEER database. We compared the 5-year disease-specific survival (DSS) between the surgery monotherapy and adjuvant RT groups for stage I (n=1697) and stage II (n=726) MCC patients. **Results:** Patients treated with surgery and adjuvant RT were younger than those who received surgery monotherapy (median age 72 versus 77, respectively). Adjuvant RT was not associated with an increase in disease-specific survival. In contrast, adjuvant RT was associated with a statistically significant decrease in 5-year DSS among stage I patients (82.8% for those treated with RT versus 87.5% for those treated with surgery monotherapy, p = 0.023). Additionally, RT was not associated with a significant increase in DSS among stage II patients (77.0% versus 74.4% for patients treated with surgery monotherapy, p=0.490). **Conclusions:** This study demonstrates that there is no statistically significant disease-specific survival benefit from adjuvant radiation therapy for stage I and II MCC in the SEER database. Interestingly, in stage I patients we find a significant negative association between adjuvant RT and DSS. Younger patients are more likely to receive adjuvant RT, which likely contributes to higher overall survival previously reported from the SEER database, but the explanation for decreased DSS in patients who received RT remains unclear. Further studies regarding the effect of radiation therapy on local disease control and tumor microenvironment are needed to establish the appropriate role of RT in stage I-II MCC patients. Research Sponsor: None.

Therapy	Adjuvant RT		Surgery Monotherapy	
Stage	I	II	I	II
N	776	411	921	315
Median Age	72	73	77	78
5-yr DSS (%)	82.8	77.0	87.5	74.4

Dynamics of circulating cytokines and chemokines during and after tumor-infiltrating lymphocyte cell therapy with lifileucel in advanced melanoma patients.

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Background: Lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, has demonstrated potentially clinically meaningful activity and durable responses in patients with advanced (unresectable or metastatic) melanoma. The regimen includes non-myeloablative lymphodepletion (NMA-LD) prior to lifileucel infusion, and a short course of interleukin-2 (IL-2) post infusion. The safety profile of the regimen is consistent with the underlying disease and the known safety profiles of NMA-LD and IL-2. Cytokine release syndrome (CRS) is an acute and severe adverse event commonly associated with chimeric antigen receptor T-cell therapy. Here, we report circulating cytokine levels during and after the lifileucel treatment to monitor immune activation, and the dynamics of cytokines and chemokines to explore mechanism of action and potential predictive clinical biomarkers. **Methods:** The full analysis set of C-144-01 (NCT02360579) includes 153 patients with unresectable or metastatic melanoma who have progressed on checkpoint inhibitors and, if applicable, BRAF/MEK inhibitors. After tumor resection, patients received NMA-LD (cyclophosphamide on Days −7 to −6 and fludarabine on Days −5 to −1) followed by a single lifileucel infusion (Day 0) and up to 6 doses of IL-2 (Days 0-4). Peripheral blood samples were collected at baseline (pre-NMA-LD and pre-lifileucel infusion) and post-lifileucel infusion on Days 1, 4, 14, 42, and 84. Serum cytokine and chemokine levels were measured with BioPlex and included a multiplex panel for IL-6, IL-7, IL-9, IL-10, IL-12, CCL2, CXCL10, IFN-γ, and TNF-α. Plasma samples also were tested for IL-6, IL-15, and IL-7 levels by ELISA. **Results:** IL-15 levels following NMA-LD peaked at Day 1 and returned to baseline by Day 42. This is consistent with prior reports that NMA-LD increases circulating IL-15 levels, which may promote TIL expansion in the absence of competing endogenous lymphocytes. Similarly, IL-7 and CCL2 also peaked at Day 1. IL-6 did not increase during or after the lifileucel regimen, consistent with absence of severe systemic inflammation including higher grade CRS after lifileucel treatment. There was no difference in cytokine and chemokine levels between responders and nonresponders in the full analysis set. **Conclusions:** These data support the hypothesized mechanism of action of NMA-LD in the lifileucel regimen. Cytokine levels measured during treatment are consistent with lack of severe systemic inflammation observed in patients treated with lifileucel. Cytokine and chemokine dynamics did not predict for response to lifileucel. Clinical trial information: NCT02360579. Research Sponsor: Iovance Biotherapeutics (San Carlos, CA, USA).

Germline pathogenic variants in a large convenience cohort of multiple melanoma subtypes.

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Background: A heritable component accounts for approximately 10% of melanomas. These estimates derive from populations deemed high risk for a germline pathogenic variant (gPV). The prevalence and clinical features of a broader melanoma patient population are unknown. **Methods:** Using the MSKCC IMPACT dataset, we identified a convenience cohort of all pts with melanoma who had undergone targeted tumor-normal sequencing (NCT01775072) for gPV in 76-90 genes. gPV were categorized by association with cancer predisposition and penetrance. **Results:** 701 pts with melanoma and germline sequencing demonstrated 105 pathogenic variants in 29 genes (Table). 14% of pts (n=99) harbored a gPV in a cancer susceptibility gene (gPV+); 49% high/moderately pathogenic, 32% low/recessive, and 19% uncertain. 6% of gPV+ pts had 2 gPVs. 77% of gPVs were involved in DNA damage repair pathways. The genes known to be associated with melanoma risk accounted for 9% of gPVs, inclusive of CDKN2A (2%), CDK 4 (1%), MITF (4%), and BRCA2 (2%). A further 15% were in genes with suggested, as yet undefined, susceptibility for melanoma; BRCA1 (6%), ATM (5%), BAP1 (2%) and PALB2 (2%). gPV+ frequency varied by melanoma subtype: unknown primary (19%, n=18), cutaneous (15%, n=64), mucosal (13%, n=13), acral (7%, n=2) and uveal (4%, n=2) (p=0.039). No significant difference in age, sex, race, stage at diagnosis, personal history of other cancer, or family history (FHx) of melanoma was seen between gPV+ and gPV-, on univariate analysis. 47% of gPV+ pts had either >1 primary melanoma, age<45 years or a FHx of melanoma (n=47), of which 14 pts had >1 risk factor. The presence of >1 melanoma and FHx of melanoma was associated with gPV+ (p=0.016). There was no significant difference in somatic TMB and MAPK pathway alterations between gPV+ and gPV-. In this cohort selected for high-risk melanomas, melanoma was the first presenting cancer for 83% of patients with gPV+. Assessment of biallelic loss to clarify if gPVs may be driving melanoma carcinogenesis is ongoing. **Conclusions:** This represents the largest cohort of sequenced matched germline and somatic analysis in melanoma. There is a 14% overall gPV prevalence that varies by melanoma subtype. The association of >1 primary melanoma, young age and a family history of melanoma with gPV+ is consistent with prior studies, however, would not capture 53% of gPV+ in this cohort. Melanoma represents the index cancer for the majority of gPVs, informing the need to expand germline testing in patients with melanoma. Research Sponsor: None.

Pathway & Gene	No. of gPVs (n=105)
DNA Damage Sensing	
CHEK2	16
ATM	5
NBN	3
Homologous Recombination Repair	
BRCA1	6
RAD51B-D	5
RECQL (4)	5
BRCA2	2
RAD50	2
PALB2	2
BAP1	2
BLM*	2
MRE11	1
BRIP1	1
Nucleotide Excision Repair	
MUTYH*	11
ERCC3	7
NTHL1*	2
Fanconi Anemia	
FANCC*	4
FANCA*	2
Cell Cycle	
MITF	4
CDK2NA	2
CDK4	1
Cell Signaling	
APC I1307K	10
NF1	2
SMARCB1	1
Citric Acid Cycle	
FH	3
SDHC	1

*Monoallelic variants that only cause disease states if biallelic.

Durability of immune checkpoint inhibitor (ICI) response following treatment discontinuation in advanced merkel cell carcinoma (MCC).

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Background: Advanced MCC has a high response rate to ICI therapy, but the durability of responses once treatment is discontinued remains unclear. We therefore reviewed the long-term outcomes of advanced MCC patients at our institution who discontinued ICI treatment after achieving favorable initial response. **Methods:** In an IRB-approved single institution retrospective review of advanced MCC patients, we analyzed all patients who received at least one dose of anti-PD(L)1 monotherapy for unresectable or metastatic disease, achieved stable disease (SD) or better, and discontinued treatment for a reason other than disease progression. Duration of response and outcomes of subsequent therapy were assessed. **Results:** Of 195 advanced MCC patients treated with ICI, we identified 45 who met study criteria. Of these, 21 (47%) had a complete response (CR) to initial ICI treatment, 23 (51%) a partial response (PR) and 1 (2%) SD. Twenty-five (56%) patients discontinued ICI electively and 20 (44%) discontinued due to toxicity. In total, 21 of the 45 patients (47%) experienced disease progression at a median of 11.2 months (range 2.1-22.7 months) from ICI cessation. The median follow-up after ICI discontinuation for patients who have not experienced progression is 22.8 months (5.8-82.0 months). There was a lower rate of progression in patients who achieved CR vs. non-CR (24% vs 67%, p=0.006) and a trend towards a lower rate in those who discontinued electively vs. due to toxicity (36% vs 60%, p=0.14). For patients in whom the molecular subtype was known, there was a higher risk for progression in patients with viral MCC (12 of 16, 75%) compared to UV-associated MCC (4 of 13, 31%, p=0.02). Fifteen of the 21 patients (71%) who experienced progression were rechallenged with ICI therapy, including both single agent (12 patients, 57%) and combination (3, 14%) therapy. The remaining patients received locally-directed therapy only (3, 14%), chemotherapy (1, 5%), declined further treatment (1, 5%), or transferred care and were lost to follow up (1, 5%). Eleven of 15 ICI-retreated patients (73%) achieved an objective response to rechallenge, including all 3 patients who received combination therapy with ipilimumab+nivolumab. Twelve of the 45 patients have expired; 6 due to progressive MCC and remaining 6 known or suspected from unrelated causes. **Conclusions:** Patients with advanced MCC have a substantial risk of disease progression following treatment discontinuation despite initial favorable ICI response, 47% in our series with a median time to event of 11.2 months, particularly in those that achieve less than a complete response. In the setting of disease progression post-ICI discontinuation, most patients maintain sensitivity to retreatment with the same drug class. Virus-positive MCC may be a risk factor for post-discontinuation relapse, which should be validated in future studies. Research Sponsor: None.

9597 Poster Session

Roginolisib, an oral, highly selective and allosteric modulator of phosphoinositide 3-kinase inhibitor delta (PI3Kδ) in patients with uveal melanoma and advanced cancers.

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Background: The highly selective, oral allosteric modulator of PI3Kδ, roginolisib (IOA-244), blocks the activity of PI3Kδ-dependent signaling, in both tumor cells and Tregs. **Methods:** Continuous daily dosing of roginolisib at 10, 20, 40 and 80 mg in patients (pts) with pretreated solid tumours and Follicular Lymphoma (FL) were evaluated (Part A). Part B consists of a dose confirmation cohort in uveal melanoma (UM) pts of 2 parts, B.1 and B.2. Primary objective: safety of the anticipated biologically effective dose (BED). Secondary objectives: PK; PD (e.g., inhibition of CD63 expression on basophils, changes in immune cell subsets in peripheral blood); RECIST 1.1 or Lugano-based responses; PFS and OS. Exploratory studies: phenotypic changes in circulating immune cells by mass cytometry (i.e., CyTOF); response assessments by radiomics; analysis of circulating protein signatures via Olink proteomics. **Results:** Part A Solid Tumour (completed): Sixteen pts were treated in 4 cohorts of 4 pts each. Pts characteristics: uveal melanoma (9/16; 56%), cutaneous melanoma (5/16; 31%) and pleural mesothelioma (2/16; 13%). Only Grade 1 and 2 AEs by CTCAE v.5 were observed, including 2 cases of transient (lasting $<$ 24 hrs) diarrhoea and 2 of AST/ALT elevation. Part A FL Cohort (completed): 8 pts were treated at 20 mg (n=4) and 80 mg (n=4). Grade 3 toxicities were transient and observed in 2/8 (25%) pts. 2/4 pts (50%) at the 80 mg had PR as per Lugano criteria. Treatment-emergent adverse events (TEAEs) did not result in study drug discontinuation, immune-related toxicity, or dose-limiting toxicity in either the solid tumor or hematological patients. UM pts (Part A and Part B)>: 29 pts (Part A: 9 pts; Part B.1: 7 pts, Part B.2: 13 pts), of which 23 were treated at 80 mg QD (RP2D). Mean time on treatment: 10.7 mo (range: 1.5-39.6 mo). ORR (RECIST 1.1): PR: 1/29 (3%); SD: 21/29 (72%). Median OS for Part A: 20.8 mo (5/9 with 4 pts alive); Part B.1 20.1 (4/7 with 3 pts alive); Part B.2 not determined; 1-year OS rate: Part A 66.7%; Part B.1 71%; Part B.2 immature. Exploratory Investigations: At 3.7 mo (Cycle 5), there were 2 groups: one with SD (13/29; 45%) and the other with PD (16/29; 55%). At 6 mo, this split continued with 38% (11/29) showing SD and 62% having PD (18/29). Volumetric changes matched durable SDs while having higher sensitivity in the 15 analyzed patients. Interestingly, tumor burden reduction in mediastinal lymph nodes was indicative of SD and 70% of pts had volumetric spleen size reduction. Volumetric and radiomic changes were matched with peripheral changes in plasma proteins and immune cell changes. **Conclusions:** Roginolisib is well tolerated at 80 mg, demonstrates efficacy, and induces phenotypic changes in circulating immune cells. At the RP2D, the most robust anti-tumour activity was observed in FL (50% PR) and UM pts (3% PR; 72% SD). Clinical trial information: NCT04328844. Research Sponsor: iOnctura SA.

The 15-gene expression profile test is independent from PRAME and 7-gene next-generation sequencing: Results from 3,267 clinically tested uveal melanomas.

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Background: The 15-gene expression profile (15-GEP) test is the gold standard in the US for metastatic risk prediction in uveal melanoma (UM). Studies have shown that the 15-GEP is superior to and independent of other clinicopathologic and molecular risk factors, including PRAME expression status and BAP1 mutation status. Supplemental tests for PRAME and the 7-gene NGS panel (*BAP1*, *SF3B1*, *EIF1AX*, *GNA11*, *GNAQ*, *CYSLTR2*, *PLCB4)*are validated and can now be run clinically from the same biopsy specimen. However, the discordance between 15-GEP, PRAME and NGS in clinical specimens is unknown. This study aimed to determine whether PRAME status or DNA mutation status could be used to predict the 15-GEP result. **Methods:** Data from fine-needle aspiration biopsy or formalin-fixed paraffin-embedded UM specimens submitted for routine comprehensive clinical testing with all three commercial tests (15-GEP, PRAME, and NGS) between February 2018 and December 2023 were collected through an Institutional Review Board-approved protocol. **Results:** Overall, 3267 tumors with comprehensive molecular testing were analyzed. 15-GEP testing yielded 65.9% (n=2152/3267) Class 1 and 34.1% (n=1115) Class 2 tumors. While Class 2 tumors were more than twice as likely to be PRAME(+) vs Class 1, 54.3% (606/1115) of Class 2 cases were PRAME(−), and 20.9% (450/2152) of Class 1 cases were PRAME(+) resulting in a PRAME/15-GEP discordance rate of 32.3% (1056/3267). Mutations in genes associated with increasing metastatic risk (*EIF1AX, SF3B1*, and *BAP1*, respectively) were identified in 58.7% (1918/3267) of cases. Most *EIF1AX* mutations (569/623, 91.3%) occurred in Class 1 tumors that were PRAME(−), while most *SF3B1*mutations were found in Class 1, PRAME(+) tumors (244/404, 60.4%). Most *BAP1* mutations (863/976, 88.4%) occurred in Class 2 (high risk) tumors, of which 53.9% (465/863) were PRAME(−). Importantly, 56.0% (1205/2152) of Class 1 tumors did not harbor detectable *EIF1AX* or *SF3B1* mutations, and 22.6% (252/1115) of Class 2 tumors did not harbor a detectable *BAP1* mutation, yielding an NGS/15-GEP discordance rate of 44.6% (1457/3267). **Conclusions:** The validated PRAME and NGS tests described here, which can be performed from the same initial biopsy sample taken for 15-GEP testing, provide results that are not systematically associated with 15-GEP class. Given that the 15-GEP has been shown to be superior to both PRAME and NGS in predicting metastatic outcomes, it is recommended that these supplemental tests only be considered in the context of a 15-GEP test result to prevent potentially over or under identifying high-risk biology. An ongoing prospective study with long term outcomes for over 1700 UM patients led by the Collaborative Ocular Oncology Group (COOG2) will provide insight into how best to effectively integrate these supplementary biomarkers with the 15-GEP class result. Research Sponsor: Castle Biosciences.

TPS9599 **Poster Session**

A phase 1/2 study to investigate the safety and efficacy of OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy in patients (pts) with advanced solid tumors.

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Background: Immune checkpoint inhibitors (ICI) have improved outcomes for pts with solid tumor malignancies; however, most pts relapse and treatment options are limited. Unengineered TIL cell therapy has shown promising efficacy in pts with ICI-resistant melanoma (1,2) and non-small cell lung cancer ([NSCLC] 3,4), but requires co-administration of systemic high-dose IL2, which is associated with safety risks and limits pt eligibility. OBX-115 TIL are engineered to express membrane-bound IL15 (mbIL15) under dose-dependent regulation using acetazolamide (ACZ), an FDA-approved small-molecule diuretic, avoiding the need for high-dose IL2. A first-in-human single-institution study (NCT05470283) evaluating the safety of OBX-115 in metastatic melanoma is ongoing. The current study (NCT06060613) is enrolling pts with solid tumors at multiple US sites using centralized manufacturing. **Methods:** This phase 1/2, single-arm, open-label, nonrandomized, multicenter study will assess the safety, tolerability, and efficacy of the OBX-115 engineered autologous TIL cell therapy regimen in pts with histologically confirmed unresectable Stage IIIC, IIID, or Stage IV metastatic melanoma (excluding uveal) with documented radiographic progression after systemic therapy containing an anti–PD-1/PD-L1 agent (if adjuvant, progression during or within 12 wks after the last dose) and received a BRAF inhibitor ± MEK inhibitor if *BRAF* V600 mutation-positive **OR** metastatic NSCLC previously treated with an approved systemic therapy for metastatic disease (including an ICI-based regimen and/or targeted therapy where applicable) and progressed, no longer deriving benefit, or unable to continue due to treatment intolerance. Pts must have ECOG PS of 0 or 1 and life expectancy >~6 months. Pts must have ≥1 lesion suitable for OBX-115 manufacturing (≥1.5 cm) and ≥1 RECIST v1.1-measurable lesion remaining after tumor tissue procurement. Primary objectives of Phase 1 are to characterize safety and tolerability and identify a recommended Phase 2 dose of OBX-115 + ACZ; Phase 2 will evaluate efficacy of the regimen (ORR using RECIST v1.1 per investigator). Cryopreserved OBX-115 is generated from the pt's own tumor tissue procured by surgical excision or core needle biopsy, and is infused after standard- (5 days) or low-dose (4 days) lymphodepletion (cyclophosphamide and fludarabine), based on clinical status. ACZ is administered at cohort-defined doses once daily for up to 10 days starting day of OBX-115 infusion, with optional ACZ redosing at Wk 6–8 for up to 10 days in pts with suboptimal radiographic response. No systemic high-dose IL2 is administered. Two sites are open and recruiting, with additional sites being activated. 1. Rohaan *NEJM* 2022. 2. Chesney *JITC* 2022. 3. Creelan *Nat Med* 2021; Schoenfeld SITC 2021. Clinical trial information: NCT06060613. Research Sponsor: Obsidian Therapeutics, Inc.

TPS9600 **Poster Session**

A phase II trial of nivolumab plus axitinib in patients with anti-PD1 refractory advanced melanoma.

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Background: A significant portion of patients (pts) with advanced melanoma (mel) either do not respond or become refractory to immune checkpoint inhibitor (ICI) therapy, with no established second line treatment regimen. A key ICI resistance mechanism includes formation of an immunosuppressive tumor microenvironment (TME). We have shown that high oxidative metabolism (OXPHOS) of mel tumor cells is associated with a hostile TME (1). Furthermore, this is associated with high intra-tumoral hypoxia (ITH). In mel tumor cells with high OXPHOS, CD8+ tumor infiltrating lymphocytes (TIL) display increased exhaustion and decreased functionality (decreased IFN-γ and TNF-α production). Pts with metastatic mel who progressed on ICI had tumor cells with high OXPHOS and ITH. Axitinib is a VEGFR small molecule tyrosine kinase inhibitor with high inhibitory activity for VEGFR 1-3. We previously showed that low dose axitinib reduces ITH in B16 murine mel, and our pre-clinical data show that axitinib synergizes with ICI to produce an improved tumor response (2). We hypothesize that axitinib will re-sensitize mel to ICI by modulating angiogenesis and reducing ITH and resultant T cell dysfunction. **Methods:** This is an investigator-initiated, single arm phase II trial of nivolumab plus axitinib for pts with unresectable stage III or IV cutaneous, acral, or mucosal mel who have progressed on prior anti-PD1 based therapy in the adjuvant or metastatic setting (NCT04493203). Pts previously treated with concomitant anti-CTLA4, anti-LAG3, BRAF/MEK inhibitors, and/or pts with brain metastases (asymptomatic or stable treated disease x 2 weeks) are eligible. Pts will receive nivolumab 480 mg IV every 4 wks with axitinib PO 5 mg twice daily for up to 2 years, or until progression or unacceptable toxicity. Pts will undergo biopsy at baseline and at 12 wks, with optional biopsy at progression. Pts will receive an oral dose of pimonidazole 0.5 mg/m^2 prior to each biopsy to permit in-vivo evaluation of ITH. Staging scans (full body PET-CT or CT and MRI brain) will be obtained at baseline, with restaging scans at 12 week intervals. Primary endpoint: overall response rate (ORR) by RECIST 1.1. Responses are determined by Blinded Independent Central Review (BICR). Secondary endpoints: safety analysis, progression-free survival (PFS) and overall survival (OS). Extensive correlative translational analyses will focus on immunophenotypic changes in the TME, ITH, profiling of tumor cell metabolism, and TIL function. The null hypothesis that the true ORR is 10% will be tested versus a one-sided alternative hypothesis of $\geq$25%, using Simon's minimax two-stage design. This design has a type I error rate 0.08 and power 0.81 when the true response rate is 0.25. PFS and OS will be estimated via Kaplan-Meier method. 31 of planned 31 pts have been enrolled in January 2024, with no data analysis yet available. 1. Najjar et al., *JCI Insight* 2019. 2. Scharping et al., *Nat Immunol* 2021. Clinical trial information: NCT04493203. Research Sponsor: Bristol-Myers Squibb; Pfizer.

TPS9601 Poster Session

Early detection of side effects in patients with metastatic melanoma receiving immune checkpoint inhibitors by investigation of CD8+ immune infiltrate with [^{89}Zr] crefmirlimab berdoxam PET.

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Background: Immune checkpoint inhibitors (ICI) improved outcomes of patients (pts) with advanced melanoma. Nevertheless, a significant number have immune-mediated adverse event (iAE). Due to the impact on quality of life and other therapeutic options, early identification of pts with increased risk of iAE is needed. CD8 immuno-PET with [^{89}Zr] crefmirlimab berdoxam (Zr-Df-IAB22M2C) has shown to be a specific tool to visualize CD8+ T cells mediating both anti-tumor immune response and inflammatory adverse effects rendering this an innovative evaluation method in the field of immuno-oncology. **Methods:** Trial design: Open-label, single-arm, single center study to determine if CD8+ T-cell infiltration evaluated by immune-PET provides diagnostic gain in early detection of severe iAE. Pts with irresectable stage III/IV melanoma receiving nivolumab + ipilimumab (NIVO+IPI) may be included. Primary objective: Feasibility of early detection of iAE by semiquantitative assessment of CD8+ T-cell infiltration using immune-PET. Secondary objectives: 1) Prediction of iAE using immuno-PET for semiquantitative assessment of CD8+ T-cell infiltration; 2) Correlation between CD8+ T-cell infiltration in metastasis and lymphoid organs and response. Baseline Imaging. To assess glucose metabolism in metastases, primary and secondary lymphatic organs [^{18}F] FDG PET/CT (60 min p.i. 1.5 MBq/KG/BW) is performed on a high sensitivity PET/CT with large field of view (Siemens Vision Quadra). Immediately after PET/CT data acquisition, pts are injected with [^{89}Zr] crefmirlimab berdoxam (37 MBq ±20%) and undergo immuno-PET/CT 24 hours p.i. to detect CD8+ T-cells in metastases and lymphoid organs. NIVO+IPI is administered immediately after completion of [^{89}Zr] crefmirlimab berdoxam-PET/CT. Blood samples are taken for immune cell composition analysis, activation state, proteomic investigation (cytokine/chemokines) as well as metabolic profile. Therapy Phase Imaging: Three weeks after first ICI cycle and before second cycle, follow-up PET/CT are performed with both radiotracers [^{18}F] FDG and [^{89}Zr] crefmirlimab berdoxam following the identical protocol described above. Clinical trial information: EudraCT number - 2021-004328-13. Research Sponsor: None.

TPS9602 **Poster Session**

A phase 3 trial of IMC-F106C (PRAME x CD3) plus nivolumab versus standard nivolumab regimens in HLA-A*02:01+ patients with previously untreated advanced melanoma (PRISM-MEL-301).

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Background: Current standard of care in newly diagnosed patients with metastatic cutaneous melanoma (CM) include anti-PD1 as monotherapy or in combination with other immune checkpoint inhibitors (ICI). However, most patients will eventually progress and the 5-year survival rate remains low, necessitating new therapies with novel mechanisms of action to combine with anti-PD1. T cell receptor (TCR) bispecifics have shown overall survival (OS) benefit with tebentafusp (gp100 ´ CD3) in a phase (Ph) 3 trial in metastatic uveal melanoma [1]. IMC-F106C is the first TCR bispecific protein targeting CD3 and PRAME (PRAME ´ CD3), redirecting T cells towards cancer cells presenting a PRAME peptide on the cell surface by HLA-A*02:01 proteins. PRAME is expressed in the vast majority of melanoma. In an ongoing Ph 1 study (NCT04262466), IMC-F106C monotherapy was well tolerated and demonstrated evidence of durable clinical activity in heavily pre-treated, advanced melanoma patients, including those who progressed on prior ICI and targeted therapy [2]. Two doses, 40 mcg and 160 mcg, were selected for further study based on exposure response modeling. Safety of combination TCR bispecifics with ICI has been demonstrated in the ongoing IMC-F106C Ph 1 study and in a prior study of tebentafusp + ICI [3]. Combining IMC-F106C with the anti-PD1 ICI nivolumab has the potential to improve progression free survival (PFS), OS, and response rate (RR). **Methods:** PRISM-MEL-301 is a randomized, global, open-label, Ph 3 study in previously untreated HLA-A*02:01+ patients with unresectable or metastatic non-uveal melanoma; up to 10% of patients can have a diagnosis of mucosal, acral, or other non-CM melanoma. The first 90 patients will be randomized 1:1:1 to receive IMC-F106C 40 mcg + nivolumab (Arm A), IMC-F106C 160 mcg + nivolumab (Arm B), or a nivolumab regimen (Arm C) from which a final IMC-F106C dose (Arm A or B) will be selected. Subsequently, approximately 590 additional patients will be randomized to Arm (A or B) vs. control Arm C, either nivolumab monotherapy or nivolumab + relatlimab, dependent on the country. Randomization will be stratified by 1) American Joint Committee on Cancer (8th Edition) M stage with lactate dehydrogenase (LDH; M0 or M1 with normal LDH vs M1 with elevated LDH); 2) prior anti-PD[L]1 adjuvant therapy (yes vs no); and 3) BRAF V600 mutation status (positive vs negative). Primary endpoint is PFS per RECIST 1.1 by blinded independent central review. Secondary endpoints include OS, ORR, and safety. Enrollment is ongoing globally. Clinical trial registration: NCT06112314 Nathan et al. N Engl J Med 2021; 385:1196 Hamid et al. Ann Oncol 2022; 33 (Supp7): S875 Hamid et al. J Immunother Cancer 2023; 11(6): e006747. Clinical trial information: NCT06112314. Research Sponsor: Immunocore.

TPS9603 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, resulting in median overall survival (OS) of <1 year. Adoptive T cell therapy, using tumor infiltrating lymphocytes (TIL), has demonstrated efficacy in treating advanced melanoma. Lifileucel (LN-144), an autologous TIL product, was recently shown to be safe and effective for patients with PD-1 refractory melanoma. However, no trials have yet explored lifileucel in patients with active MBM. **Methods:** This single-center pilot trial (NCT05640193) aims to enroll 10 pts with asymptomatic MBM from non-uveal melanoma to receive lifileucel. Patients must have ≥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 ≤1, ≥1 resectable lesion(s) (≥1.5 cm), recovered from prior surgery/anticancer treatment-related AEs (grade ≤1). Patients are ineligible if they have symptomatic MBM and/or require corticosteroids of ≥10 mg/day of prednisone or equivalent. Lifileucel is generated from resected tumor in a centralized GMP process. The regimen includes nonmyeloablative lymphodepletion with cyclophosphamide 750 mg/m^2 on days 1-3 and fludarabine 30 mg/kg on days 1-4 (reduced dose compared with standard lifileucel protocol), lifileucel infusion, and up to 6 doses of high-dose IL-2. The primary endpoint is feasibility, defined as ≥7/10 patients who undergo tumor resection successfully 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, the ASCO Foundation; Melanoma Research Foundation.

TPS9604 Poster Session

A randomized, controlled, multicenter, phase 3 study of vusolimogene oderparepvec (VO) combined with nivolumab vs treatment of physician's choice in patients with advanced melanoma that has progressed on anti–PD-1 and anti–CTLA-4 therapy (IGNYTE-3).

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Background: Melanoma is the 5th most common cancer type, with ~100,000 new cases and ~8,000 deaths estimated in the US for 2024. First-line systemic treatment with immune checkpoint inhibitors improved the objective response rate (ORR) and extended progression-free survival (PFS) and overall survival (OS) for patients with advanced disease. The combination of anti–PD-1 nivolumab (nivo) + anti–CTLA-4 ipilimumab (ipi) therapy is associated with the highest ORR and best PFS and OS in this setting. However, only about half of patients respond, and there is no standard of care for patients who progress after anti–PD-1–based therapy. VO (also referred to as RP1) is a selectively replication-competent HSV-1 oncolytic virus that expresses human GM-CSF and a fusogenic glycoprotein (GALV-GP-R–). Preliminary data from the phase 1/2 study (IGNYTE) showed that intratumoral (IT) VO plus intravenous (IV) nivolumab (nivo) was well tolerated and had meaningful antitumor activity (ORR, 31.4%) with durable responses in patients with advanced melanoma who progressed on prior anti–PD-1 therapy. This phase 3 study will evaluate the overall survival and clinical benefit as well as the safety of VO plus nivo for patients with advanced melanoma whose disease has progressed after receiving anti–PD-1 and anti–CTLA-4 therapy (or who are not eligible for anti–CTLA-4 therapy in addition to anti–PD-1) versus physician's choice. **Methods:** This is a randomized, controlled, multicenter, phase 3 clinical trial comparing VO in combination with nivo vs physician's choice of treatment in patients with unresectable or metastatic melanoma. Key eligibility criteria include age ≥12 years, stage IIIb–IV/M1a–M1d cutaneous melanoma, confirmed disease progression on an anti–PD–1 and anti–CTLA-4 treatment (administered in combination or in sequence with anti–PD-1 last), at least 1 measurable tumor (≥1 cm), and adequate hematologic, hepatic, and renal function. Patients who are not candidates for anti–CTLA-4 therapy may enroll if they have confirmed progression on anti–PD-1 therapy. Patients with *BRAF* V600 mutant melanoma must have received an anti-BRAF + anti-MEK targeted therapy prior to enrollment. Patients (N = ~400) will be randomized 1:1 to receive VO plus nivo or physician's choice (nivo + relatlimab, anti–PD–1 monotherapy rechallenge [nivo or pembrolizumab], or single-agent chemotherapy [dacarbazine, temozolomide, or paclitaxel/albumin-bound paclitaxel]). VO is given IT Q2W; nivo is administered IV at 240 mg Q2W or 480 mg Q4W starting with the 2nd dose of VO. The primary endpoint of the study is OS; the key secondary endpoints are PFS and ORR. Additional endpoints include complete response rate, duration of response, disease control rate, and safety. Clinical trial information: NCT06264180. Research Sponsor: Replimune, Inc.

TPS9605 **Poster Session**

A phase 2 trial of IO102-IO103 and nivolumab-relatlimab fixed-dose combination in previously untreated, unresectable melanoma.

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Background: One emerging strategy to augment immune checkpoint inhibitor efficacy is to eliminate immunosuppressive cell populations in the tumor microenvironment (TME) through vaccination. IO102-IO103 is an investigational cancer vaccine that targets both tumor and immune-suppressive cells in the TME. IO102-IO103 treatment promotes inflammation and potentiates anti-tumor activity via activation and expansion of T cells against IDO1 and/or PD-L1 positive cells. IO102-IO103 plus nivolumab demonstrated an impressive objective response rate (ORR) of 80% in the phase 1/2 MM1636 trial of 30 patients with previously untreated, unresectable melanoma, and a randomized phase 3 trial of pembrolizumab with or without IO102-IO103 (NCT05155254) is ongoing. No prior studies have evaluated IO102-IO103 in combination with dual PD-1 and LAG-3 blockade with nivolumab-relatlimab (nivo-rela), and to our knowledge there are no existing clinical data for other investigational agents in combination with nivo-rela. **Methods:** NCT05912244 is a single-arm, investigator-initiated trial testing IO102-IO103 in combination with nivo-rela in patients with previously untreated, unresectable melanoma. Twelve of forty-three planned patients have been enrolled. All patients will be treated with nivo-rela every four weeks for up to two years. IO102-IO103 will be administered subcutaneously every two weeks for the initial eight weeks, and then every four weeks for up to two years. An interim efficacy analysis for futility will be performed after response data are available for 21 patients. Eligible patients must have histologically confirmed, unresectable stage III or stage IV non-uveal melanoma, measurable disease by RECIST v1.1, an ECOG performance status of 0 or 1, and definitive treatment of any brain metastases. Prior systemic treatment in the neoadjuvant or adjuvant setting is allowed if completed at least six months prior to trial enrollment. Available pre-treatment melanoma tissue is required, and all patients will undergo an on-treatment study biopsy between the second and third dose of nivo-rela. Peripheral blood mononuclear cells will be collected prior to the first three doses of nivo-rela. The primary endpoint is ORR by RECIST v1.1, weighted by PD-L1 expression. Secondary endpoints include safety assessed by Common Terminology Criteria for Adverse Events v 5.0, progression-free survival (PFS) by RECIST v1.1, duration of disease response, and disease control rate. Exploratory correlative endpoints include assessment of changes in PD-L1 and IDO-expressing cells in the TME on paired tumor biopsies, identification of peripheral PD-L1 and IDO-reactive cells in the peripheral blood by ELISpot, and assessment of peripheral pre-treatment and on-treatment T cell clonality by TCR sequencing. Clinical trial information: NCT05912244. Research Sponsor: IO Biotech ApS; National Cancer Institute; P30CA008748.

TPS9606 **Poster Session**

A phase III, open-label, multicenter, randomized controlled trial of tunlametinib versus investigator-selected chemotherapy in patients with advanced NRAS-mutant melanoma who had previously received immunotherapy.

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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) has showed an encouraging efficacy (confirmed ORR:34.8%, mPFS:4.2 months) with a manageable safety profile in phase II pivotal registrational study, which was published in ASCO 2023 annal meeting (NO.:9510). Here, we present the design of phase III randomized controlled study. **Methods:** This is a multicenter, two-arm, open-label, randomized controlled phase III confirmatory clinical trial to evaluate the efficacy and safety of tunlametinib in comparison with the combination chemotherapy of investigator's choice in advanced NRAS-mutant melanoma patients who had previously received immunotherapy. A total of 165 subjects from about 12 sites in China will be included and randomly assigned to the corresponding treatment group in 2:1 ratio. Two stratification factors before randomization: LDH level and whether have received chemotherapy. The key inclusion criteria included: a) Patients with unresectable stage III or metastatic IV melanoma confirmed by histology or cytology; b) History of immunotherapy failure or could not tolerate immunotherapy; c) Be able to provide NRAS mutation positive test report at baseline and provide sufficient histological specimens for NRAS mutation confirmation by central laboratory. Experimental group subjects will receive continuous administration of tunlametinib 12mg BID, 28 days per cycle. Control group subjects will receive one of the following regimens which according to investigator's choice (paclitaxel plus carboplatin, or temozolomide plus cisplatin, or dacarbazine plus cisplatin) , 28 days per cycle. The two groups will receive continuous therapy until disease progression or intolerable toxicity. The primary endpoint is progression-free survival which assessed by independent radiology review committee. Secondary endpoints included overall survival, objective response rate, disease control rate, duration of response, safety, pharmacokinetics and exposure-response. Exploratory endpoints are to evaluate quality of life between two groups and to development a companion diagnostic kit for NRAS gene mutations detection. This study is currently open for enrollment. Clinical trial information: NCT06008106. Research Sponsor: Shanghai KeChow Pharma.

TPS9607 **Poster Session**

Randomized phase II trial of pembrolizumab/lenvatinib (P+L) +/- responder fecal microbiota transplant (R-FMT) in PD-1 relapsed/refractory (R/R) cutaneous melanoma (MEL).

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Background: A significant portion of patients (pts) with advanced MEL develop resistance to immune checkpoint inhibitors (ICI). The gut microbiome is a major tumor-extrinsic regulator of ICI response. In mice, gut microbiota modulate therapeutic activity of ICI, and administration of certain gut commensals or responder-derived fecal microbiota transplantation (R-FMT) promotes anti-PD-1 efficacy in melanoma-bearing mice. In the LEAP-004 trial, P+L produced 21% ORR in PD-1 R/R MEL with Gr3+ TRAE 45.6%. Longitudinal analyses of gut microbiome samples from ICI-treated cancer pts suggests key species including Actinobacteria and Firmicutes are associated with favorable response. We and others have previously demonstrated that microbiome modulation using R-FMT reversed PD-1 non-response in PD-1 R/R MEL. In PD-1 naïve MEL, healthy donor FMT (hdFMT) augments benefit of PD-1 monotherapy. We hypothesized that intestinal dysbiosis mediates PD-1 resistance in PD-1 R/R MEL, microbiome modulation may reverse TKI toxicity, and that R-FMT may resensitize MEL to PD-1 blockade. **Methods:** This is an investigator-initiated, randomized, phase II trial of P+L vs. P+L+R-FMT in PD-1 R/R MEL. Pts must have measurable disease per RECIST v1.1, no active CNS metastases (or if present, previously treated and stable on repeat imaging), and no contraindications to FMT administration. R-FMT is derived from non-obese, advanced MEL with durable response (mPFS ≥24 months) following prior PD-1 ICI, with no recent (≤1 month) antibiotic exposure. Donors are screened broadly for infectious agents including SARS-CoV-2 using bookend screening. R-FMT is processed to make fecal infusates and orally bioavailable capsules. Eligible pts are randomized 1:1 to either P+L [P 200mg every 3 weeks (Q3W) along with L 20mg orally once daily] or P+L+R-FMT. R-FMT is administered endoscopically on D1, and D42, and thereafter via capsules until progression or unacceptable toxicity. Response is assessed at D73, and thereafter Q12W. Pts undergo biopsies at baseline and W8, with optional biopsy at progression. Primary endpoint: ORR assessed using RECIST v1.1 by Blinded Independent Central Review (BICR). Secondary endpoints include: safety, progression-free survival (PFS), overall survival (OS), and landmark PFS/OS. Key translational endpoints include immune activation (tumor tissue, blood), metagenomic engraftment, and transcriptomic analyses of intestinal luminal myeloid cells and exfoliome. The null hypothesis that the true ORR is 20% will be tested versus a one-sided alternative hypothesis of ≥50%. This design has a type I error rate 0.10 and power 0.8 when the true response rate is 0.25. Enrollment has commenced. Clinical trial information: NCT06030037. Research Sponsor: National Cancer Institute; U0 CA268806; Gateway Foundation for Cancer Research.

TPS9608 **Poster Session**

Reduced dose fludarabine/cyclophosphamide lymphodepletion for tumor-infiltrating lymphocytes therapy (LN-144, lifileucel) in metastatic melanoma.

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Background: Metastatic melanoma (MM) patients who have progressed following immune checkpoint inhibitors (ICI; anti–PD-1/CTLA-4 therapy) and targeted agents (BRAF/MEK inhibitors) have limited treatment options and dismal prognosis. An autologous tumor-infiltrating lymphocytes (TIL) therapy (LN-144, lifileucel) has demonstrated efficacy and durable responses in heavily pretreated advanced melanoma. In a phase II study of TIL therapy (lifileucel) with traditional lymphodepletion (LD), using fludarabine 25 mg/m2 for 5 days and cyclophosphamide (Cy) 60 mg/kg for 2 days, in 153 MM patients previously treated with ICI and BRAF/MEK inhibitors, an overall response rate (ORR) of 31% was noted, and the median duration of response (DOR) was not reached after 27.6 month follow up. We hypothesize that a reduced dose of Flu/Cy LD for TIL therapy will have similar TIL expansion and persistence post-infusion, resulting in similar efficacy with a reduced toxicity profile. **Methods:** Study NCT06151847 is a single-center, open-label phase II pilot trial evaluating the efficacy, in vivo persistence, and safety of TIL therapy after reduced dose Flu/Cy LD. Key inclusion criteria include unresectable or metastatic melanoma (stage IIIC-IV) with disease progression after one or more lines of therapy. Four of the 12 planned patients have been enrolled as of February 2, 2024. Central TIL manufacturing from at least a 1.5 cm tumor specimen involves ex vivo expansion through cell culture in the presence of the interleukin (IL)-2 and an anti-CD3 monoclonal antibody (1-150 $x10^9$ viable cells). Patients will receive an outpatient reduced-dose Flu/Cy LD regimen of Flu (30 mg/m^2 on days -4, -3, -2, -1) and Cy (750 mg/m^2 on days -4, -3, -2). Infusion of TIL will be performed on day 0 followed by high-dose IL-2 (600,000 IU/kg up to 6 doses). The primary objective will be to ascertain TIL persistence using T-cell receptor (TCR) sequencing at day 42 which will be compared to historical data already generated utilizing traditional Flu/Cy LD. The secondary objectives will be to evaluate the efficacy parameters including ORR, DOR, progression-free survival (PFS), and overall survival (OS), and the safety profile of TIL in combination with a reduced dose Flu/Cy LD regimen. Exploratory objectives will involvecorrelative analyses to characterize the immunome and microenvironment. If TIL persistence is roughly equivocal between the reduced and high-dose Flu/Cy LD regimens, the design of a larger-scale trial using reduced-dose Flu/Cy LD for TIL therapy may be considered. Study follow-up will continue for one year. Clinical trial information: NCT06151847. Research Sponsor: Iovance Biotherapeutics, Inc.

TPS9609 **Poster Session**

Novel RNA-nanoparticle vaccine for the treatment of early melanoma recurrence following adjuvant anti-PD-1 antibody therapy.

Bently Patrick Doonan, Christiana M. Shaw, Ji-Hyun Lee, Eugenio Simon Manso, Hector Mendez-Gomez, Christina Von Roemeling, Duane Anthony Mitchell, Elias Sayour, Thomas J. George; University of Florida College of Medicine, Gainesville, FL; University of Florida Department of Surgery, Gainesville, FL; Department of Biostatistics, University of Florida College of Public Health and Health Professions & College of Medicine, Gainesville, FL; University of Florida, Gainesville, FL; University of Florida Brain Tumor Immunotherapy Program, Preston A. Wells, Jr. Center for Brain Tumor Therapy, Gainesville, FL; University of Florida Health Cancer Center, Gainesville, FL

Background: Melanoma is a major public health concern with an anticipated increase in prevalence and incidence in the coming years. Early detection and surgical management remain the mainstay of treatment of early-stage disease and use of adjuvant immunotherapy has improved outcomes for patients with more aggressive (IIB-IIC) local disease or those with lymph node involvement (IIIA-IIID). Based on the tolerability and efficacy across subjects with both BRAF mutated and wildtype melanoma anti-PD1 (aPD1) therapy with either nivolumab or pembrolizumab are considered first line treatment in this setting. Adjuvant aPD1 therapy has significant improvement in relapse free survival (RFS) yet 25-30% of subjects will have disease recurrence within 1 year of surgery. When disease recurs, the response rate to immunotherapy is significantly reduced, re-challenged with aPD1 therapy has shown an Objective Response Rate (ORR) of zero and a marginally better response to CTLA-4 blockade. Novel strategies are needed for this at-risk population with early aPD1 resistance. To address this need we have developed a novel multi-lamellar lipid-nanoparticle complexed with total-tumor derived mRNA administered intravenously to restore responsiveness to aPD1 through reprogramming the tumor microenvironment (TME) bridging an innate and adaptive immune response. We have designed a clinical trial in which patients who progress on while on aPD1 therapy or within 6 months of therapy will have tumor sampled and a personalized lipid-nanoparticle vaccine generated. This vaccine is then administered IV for a total of 3 doses spanning 6 weeks to reprogram the TME and restore response to aPD1 which will be resumed on completion of vaccine series. This phase I study will assess initial feasibility and safety of vaccine generation, utilize ctDNA surveillance as early detection of adjuvant failure, and provide essential biologic information on immunotherapy resistance to aPD1 therapy. **Methods:** We have designed a modified 3+3 phase I clinical trial that will enroll subjects who have evidence of progressive disease (PD) by ctDNA and/or RECIST 1.1 criteria while receiving adjuvant aPD1 therapy, or those who progress within 6 months of completion of treatment for stage IIB-IIID melanoma. The goal of this study is to assess safety, tolerability, and feasibility of tumor specific RNA-LPs. Important biological correlates will also be collected and analyzed including tumor tissue sampling at initial time of checkpoint resistance and following vaccination series to identify key changes to the TME and tumor induced by lipid-nanoparticle vaccine administration. Clinical trial information: NCT05264974. Research Sponsor: Florida Department of Health James and Esther King Biomedical Research Program.

TPS9610 **Poster Session**

A phase I/IIa of [^{212}Pb]VMT01 targeted a-particle therapy for unresectable or metastatic melanoma.

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Background: Melanoma is an aggressive skin cancer with potential to metastasize early in disease development. Unresectable and metastatic melanoma accounts for 12% of cases and, despite recent advances in treatment, 5-year overall survival for this disease remains low at 35%. The melanocortin 1 receptor (MC1R) is highly expressed in melanoma with low expression in normal tissues and is therefore a target for radiopharmaceutical therapy. We developed [^{212}Pb]VMT01, a MC1R-targeting peptide conjugated to a lead-specific chelator. Targeted therapy with ^{212}Pb has the potential to be efficacious due to the high relative biological effectiveness of α-particles emitted upon its decay. The short physical half-life of ^{212}Pb (10.6 h) and fast tumor targeting and clearance properties of [^{212}Pb]VMT01 can achieve highly efficient delivery of α-particles to MC1R-expressing cancers while sparing healthy tissues. We hypothesize that [^{212}Pb]VMT01 can be safely administered to patients with metastatic or unresectable melanoma and can enable disease control. **Methods:** This is an open-label, multi-center, dose-escalation/dose expansion, phase I/IIa clinical trial evaluating the safety, tolerability, pharmacokinetics, and efficacy of [^{212}Pb]VMT01 (NCT05655312). Phase I of the trial follows a mTPI-2 design. The first two cohorts incorporate dosimetry, where participants receive up to 925 MBq or 278 MBq of the therapeutic surrogate [^{203}Pb]VMT01 or [^{68}Ga]VMT02, respectively, prior to receiving treatment cycles. In these participants, SPECT/CT or PET/CT imaging is obtained up to 24 hours post-injection. Up to 3 treatment cycles of [^{212}Pb]VMT01, co-administered with renal protective amino acids, are given 8 weeks apart, with a dose-limiting toxicity observation period of 6 weeks. The cohort 1 dose was 111 MBq, while the ongoing cohort 2 utilizes 185 MBq. Eligibility criteria include MC1R+ disease as determined by SPECT or PET, melanoma stage III or IV and progressive disease by RECIST 1.1. Study participants must have progressed on at least one prior SOC therapy. As part of the study, CT and/or MRI, and FDG PET are acquired at baseline, during, and at the end of treatment. Safety is assessed weekly during cycle 1 and bi-weekly for subsequent cycles. The total in-trial follow-up period is 18 months following final administration of drug. Efficacy is assessed by RECIST 1.1 criteria. The primary objectives are evaluation of the safety of [^{212}Pb]VMT01, determination of the maximum tolerated or maximum feasible dose, and determination of the anti-tumor efficacy of [^{212}Pb]. All primary, secondary, and exploratory objectives' data will be collected for all participants. An interim futility evaluation may be performed after ~10 participants in the dose escalation phase for participants who have completed their first post-treatment response assessment. The trial is open for recruitment. Clinical trial information: NCT05655312. Research Sponsor: None.

TPS9611 **Poster Session**

A phase 3 trial of fixed dose combinations of fianlimab (anti–LAG-3) + cemiplimab (anti–PD-1) versus relatlimab + nivolumab in patients with unresectable 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 high-affinity, fully human, immunoglobulin G4 monoclonal antibodies. Concurrent LAG-3 blockade may enhance the efficacy of anti–PD-1 therapies. Relatlimab (anti–LAG-3) + nivolumab (anti–PD-1) monoclonal antibodies demonstrated benefit in progression-free survival (PFS) in advanced melanoma (Mel) patients compared with nivolumab alone in the RELATIVITY-047 study. In a multicohort Phase 1 study (NCT03005782), fianlimab + cemiplimab demonstrated reproducibly high clinical activity (objective response rate [ORR]: 61%, N=98) in three independent cohorts of advanced PD-(L)1–naïve metastatic Mel patients with an acceptable safety profile. **Methods:** This is a randomized, open-label, multicenter Phase 3 study (NCT06246916) comparing the fixed dose combination (FDC) of fianlimab + cemiplimab to the FDC of relatlimab + nivolumab in patients with unresectable or metastatic Mel. The primary objective is to demonstrate superiority of fianlimab + cemiplimab compared with relatlimab + nivolumab as measured by ORR assessed by blinded independent central review (BICR). This study will be conducted at approximately 80 sites across North America. Key inclusion criteria are: (1) aged ≥18 years; (2) histologically confirmed unresectable stage III or IV (metastatic) Mel; (3) no prior systemic therapy for unresectable or metastatic Mel; patients with adjuvant and/or neoadjuvant systemic therapies are eligible with a treatment-free and disease-free interval of >6 months; (4) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; (5) Eastern Cooperative Oncology Group performance status of ≤1; (6) adequate bone marrow, hepatic, and kidney function. Approximately 560 patients will be randomized in a 1:1 ratio to two treatment arms: Arm A: FDC of fianlimab (Dose 1) + cemiplimab (Dose 2) every 3 weeks intravenously (IV); Arm B: FDC of relatlimab 160 mg + nivolumab 480 mg every 4 weeks IV. All patients will be stratified based on metastatic stage (stage III vs M1a–b vs M1c–d), baseline lactate dehydrogenase level (≤ vs > upper limit of normal), and prior adjuvant and/or neoadjuvant systemic therapy. Patients will receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, a study withdrawal criterion is met, or the sponsor terminates the study. The primary endpoint is ORR and key secondary endpoints are PFS and overall survival. Additional secondary endpoints are duration of response, disease control rate, investigator-assessed ORR and PFS, safety, pharmacokinetics, and immunogenicity. Clinical trial information: NCT06246916. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS9612 **Poster Session**

First-in-human study of ^{225}actinium mti-201 (^{225}Ac-MTI-201) in metastatic uveal melanoma (UM).

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Background: Prognosis in metastatic uveal melanoma (UM) has historically been poor approximating 1 year from diagnosis. Tebentafusp is the only approved systemic agent for HLA-A*02:01 positive metastatic UM, and novel therapies are needed. The melanocortin-1 receptor (MC1R) receptor is highly expressed in UM with limited expression in normal tissues. Actinium-225 (^{225}Ac) is an alpha particle emitting radionuclide ideal for targeted ligand binding due to high linear energy transfer and limited free path ($<$100 μm) in tissue. We developed a novel MC1R targeted radiopharmaceutical ^{225}Ac-MTI-201, and demonstrated high biostability, affinity, MC1R-specific cytotoxicity with defined dosimetry and pharmacokinetics in pre-clinical studies (1). Murine efficacy studies of UM showed significant delay of tumor growth and improved survival compared to controls. **Methods:** This is a single institution first-in-human phase I study (NCT05496686) of ^{225}Ac-MTI-201 in metastatic UM. The primary objective is to determine the safety of a single intravenous dose of ^{225}Ac-MTI-201 relative to radioactivity dose. Secondary endpoints include 1) pharmacokinetics (PK) and clearance of ^{225}Ac-MTI-201, 2) objective response rate and duration, progression-free survival, and overall survival in metastatic UM. Salient eligibility criteria include: 1) age $\geq$18 years; 2) histologically confirmed metastatic UM with progression after at least 1 prior line of therapy; 3) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; 4) Eastern Cooperative Oncology Group performance status of $\leq$1; 5) adequate marrow, renal and hepatic function; 6) no more than 25% of bone marrow treated with prior radiotherapy. Patients will receive a single dose of ^{225}Ac-MTI-201 under appropriate guidelines and precautions for administration of radiopharmaceuticals. Pre-injection and post-injection PK sampling at defined intervals are undertaken. There are 12 dose levels for ^{225}Ac-MTI-201 being investigated ranging from 4.7 microcurie (μCi) to 1327 μCi. Dose escalation is done using a modified continual re-assessment method with a cohort size of one based on dose limiting toxicity (DLT) assessment within 28 days of drug administration using CTCAE v5.0. Definitions of DLT include G4 neutropenia or febrile neutropenia, G4 thrombocytopenia or G3 thrombocytopenia with clinically significant bleeding, $>$ G3 non-hematological toxicity with selected exceptions, laboratory abnormalities that satisfy Hy's law, or any death not related to underlying disease or extraneous cause. Response assessments are undertaken with cross-sectional imaging every 8 weeks in year 1, and every 12 weeks in year 2. This study is currently open for enrollment. Dose levels 1-4 have been completed without DLT. 1. Tafreshi, J Nucl Med 2019. Clinical trial information: NCT05496686. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; HHSN261201700035C; Modulation Therapeutics.

TPS9613 Poster Session

A phase 2 study to determine the pathological (path) response to neoadjuvant nivolumab (nivo) and relatlimab (rela) in stage I to III resectable Merkel cell carcinoma (Neo-MCC).

Maria Gonzalez, Alexander Christopher Jonathan van Akkooi, Sydney Ch'ng, Kerwin Frank Shannon, Andrew John Spillane, Jonathan Stretch, Michael Alexander Rtshiladze, Thomas Pennington, David Coker, Robyn P.M. Saw, Rony Kapoor, Edward Hsiao, Robert V Rawson, Monica Osorio, Alexander M. Menzies, Serigne N Lo, Richard A Scolyer, Angela M Hong, Georgina V. Long, Ines Esteves Domingues Pires Da Silva; Melanoma Institute Australia, Sydney, NSW, Australia; Melanoma Institute Australia, Wollstonecraft, NSW, Australia; Melanoma Institute Australia, Royal Prince Alfred Hospital, Chris O'Brien Lifehouse, The University of Sydney, The Mater Hospital Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Chris O'Brien Lifehouse, Sydney, NSW, Australia; Melanoma Institute Australia, Sydney, Australia; Melanoma Institute Australia, Mater Hospital, Royal Prince Alfred Hospital, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Royal Prince Alfred Hospital, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, Royal Prince Alfred Hospital, The Mater Hospital Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, I-Med Radiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, Royal North Shore Hospital, Department of Nuclear Medicine and PET, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Blacktown Hospital, Sydney, NSW, Australia

Background: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine cancer of the skin with viral and sun related aetiologies, and an overall mortality rate twice that observed in cutaneous melanoma (33% vs 15%). The 5-year disease specific survival is 60% to 87% for those presenting with local disease, 39% to 62% for nodal disease and 11% to 20% for metastatic disease (1). Neoadjuvant therapy (NAT) is a powerful treatment platform to rapidly assess drug activity in resectable cancers. In melanoma, using International Neoadjuvant Melanoma Consortium (INMC) path response criteria (2), a major path response to immunotherapy (≤10% viable tumor) correlates with low risk of recurrence in resectable stage III disease (Menzies et al., 2021), and improved survival and EFS when immunotherapy is given neoadjuvantly as compared to adjuvant (adj) treatment (Patel et al., 2022). In a study of NAT anti-PD1 monotherapy with nivolumab, in patients (pts) with resectable IIA-IV MCC (N=36), 47.2% of pts achieved a complete path response (pCR) (Topalian et al., 2020). Other benefits of NAT 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. The Neo-MCC 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 in pts with resectable stage I-III MCC. **Methods:** Pts with histologically confirmed resectable clinical stage I (≥ 10 mm), II or III Merkel cell carcinoma, are eligible (N=20). All pts undergo complete resection (RES) at wk 6 following NAT with 2 doses of nivo (480 mg, IV) plus rela (160 mg, IV) at wk 0 and 4. Standard of care sentinel lymph node biopsy will be completed as indicated. Pts with non-path response (>50% viable tumor) or partial path response (>10% - ≤50% viable tumor) at RES will receive adj radiotherapy (RT) to all disease sites, including the draining lymph node basin. Pts with pCR (0% viable tumor) or near-pCR response (≤10% viable tumor) will receive no further adj treatment. Pts with involved RES path margins will be considered for adj RT, following multidisciplinary team consultation to determine the role of further surgery. CT, and FDG PET/CT will be performed at baseline (BL), prior to RES to measure NAT response, and 6-monthly over a 10-year follow-up period. Tumor 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 NAT using INMC response criteria. Secondary endpoints include RFS, OS, safety/tolerability, surgical outcomes, QOL, and biomarker analyses. 1. Mistry, et al., 2022. 2. Tetzlaff et al., 2018. Clinical trial information: NCT06151236. Research Sponsor: Melanoma Institute Australia and Bristol Myers Squibb.

TPS9614 Poster Session

A phase 1/2 study of vusolimogene oderparepvec (RP1) in primary melanoma (mel) to reduce the risk of sentinel lymph node (SLN) metastasis.

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Background: The majority of the 80,000 newly diagnosed mel patients in the US have localized early-stage disease and undergo wide local excision (WLE) with or without SLN biopsy. The SLN is a critical prognostic marker and pivotal to immune response initiation, and fosters tumor-mediated immune suppression and pre-metastatic niches. Thus, SLN is a key target for local immune intervention. Vusolimogene oderparepvec (RP1), a locally administered oncolytic immunotherapy, provides a unique opportunity for intervention following mel diagnosis, prior to definitive surgical management. Derived from the HSV1 strain RH018A, RP1 exhibits superior killing on human tumor cell lines, designed with deletions in neurovirulence factors (ICP34.5 and ICP47) and immune-stimulating elements (increased US11 expression, GM-CSF and GALV-GP R-) to maximize oncolytic potency and induce cell death. Preclinical and clinical data demonstrate RP1's robust antitumor efficacy in advanced mel. This trial addresses a crucial gap in understanding RP1's impact on SLN dynamics, holding promise for preventing disease recurrence in this high-risk population. We hypothesize that in mel patients with high risk, clinically node negative disease (pT3b-T4b), administration of RP1 will reduce rates of SLN positivity compared to a historic control by favorably reshaping the immune landscape of the primary tumor, SLN and peripheral blood. **Methods:** This investigator-initiated, single site, open label, non-randomized phase 1/2 pilot study (NCT06216938) will enroll 25 patients with high-risk, clinically node-negative mel (pT3b-T4b). Major eligibility criteria include diagnosis of pT3b, T4a, or T4b non-uveal mel with visible residual tumor or positive initial biopsy margins, ECOG 0 or 1 and adequate organ function on screening labs. Patients will receive 3 doses (1ml/dose) of RP1, locally injected at the primary tumor site before standard WLE and SLN biopsy (SLNB). The first dose on day 1 will be 10e6 pfu/ml, followed by 10e7 pfu/ml for the next two doses on days 15 and 21, administered over 4-5 weeks before WLE and SLNB. Surgery occurs within 35 days of the 1st RP1 injection to avoid delays in definitive treatment. Biopsies and blood samples are obtained pre- and post-treatment. Patients will be followed for up to 3 years. Safety assessments include physical exams, labs, and adverse events (AE) monitoring. The primary endpoint is the rate of SLN positivity in the overall cohort, calculated by comparing the observed rates to the expected number of positive SLNs for that cohort using the Melanoma Institute of Australia's Prediction Tool. Secondary endpoints include safety and tolerability of RP1, RFS and OS. Exploratory correlative assays will compare the immunophenotype in primary tumor and the SLN (IHC) and in peripheral blood (flow cytometry) between baseline and on treatment. Clinical trial information: NCT06216938. Research Sponsor: None.

TPS9615 **Poster Session**

The MARIANE-trial: Multicenter phase 1b/2 trial testing safety and efficacy of neoadjuvant intradermal ipilimumab and nivolumab in high-risk stage II melanoma.

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Background: Adjuvant anti-PD1 (nivolumab or pembrolizumab) has been shown to improve relapse free survival for patients with high-risk stage II melanoma (IIB-C). However, this therapy probably won't be reimbursed as standard of care in most European countries due to high costs, and the benefit-risk-ratio. For macroscopic stage III melanoma, neoadjuvant ipilimumab (IPI; anti-CTLA4) plus nivolumab (NIVO; anti-PD1) has been shown to induce high pathologic response rates in the resected lymph nodes, long-term event free survival, and this schedule is currently being compared to adjuvant NIVO in a phase 3 study (NCT04949113). This combination schedule, however, is unsuitable for earlier disease stages, due to high costs and clinical toxicity. In preclinical models, a local tumor draining lymph node directed delivery of anti-PD-1 plus anti-CTLA-4 has been demonstrated to outperform systemic administration on induction of T-cell proliferation and tumor control. In patients, local delivery of anti-PD-1 or anti-CTLA-4 has been suggested to be equally effective in tumor control with a reduction of adverse events. These data have formed the rationale for testing intradermal injections at the excision site of the primary tumor with IPI and NIVO prior to the re-excision and sentinel node procedure in high-risk stage II melanoma patients. **Methods:** This multicenter, dose-escalating phase Ib/II trial, using a Simon's two-stage design, is the first trial to test feasibility and efficacy of intradermal IPI plus NIVO in high-risk stage II melanoma patients. In total 21 to 80 patients, diagnosed with a stage T3-4 cutaneous melanoma with $\geq$ 50% chance of positive sentinel node, naïve for re-excision, sentinel node surgery and immunotherapy, will be included in this trial. Patients will receive 2 cycles of intradermal IPI 0.5 mg + NIVO 1 mg at the excision site of the primary melanoma (every 3 weeks; arm A); 6 cycles intradermal IPI 0.5 mg + NIVO 1 mg (every week; arm B); 2 cycles intradermal IPI 10 mg + NIVO 20 mg (every 3 weeks, arm C); or 2 cycles of intravenous nivolumab 240 mg every 3 weeks combined with the most optimal intradermal regimen of IPI + NIVO (based on the results of arm A, B or C) in arm D. In week 6, patients will undergo sentinel node surgery, whereafter only patients with a non-MPR (>10% vital tumor) will be treated with adjuvant anti-PD1 according to current standard of care. We expect the first patient to be enrolled in March 2024and to be accruing for 1-1.5 years. Clinical trial information: NCT06240143. Research Sponsor: NKI-AvL.

TPS9616 **Poster Session**

INTerpath-001: Pembrolizumab with V940 (mRNA-4157) versus pembrolizumab with placebo for adjuvant treatment of high-risk stage II-IV melanoma.

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Background: The anti–PD-1 antibody pembrolizumab is approved as adjuvant therapy for stage IIB-C and stage III melanoma by AJCC 8th ed, following complete resection. Adjuvant pembrolizumab has improved recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) in patients with high-risk melanoma, but many patients experience disease recurrence. In the randomized phase 2b KEYNOTE-942 study, the individualized neoantigen therapy V940 showed improved RFS and DMFS when used in combination with pembrolizumab versus pembrolizumab monotherapy in patients with stage III or IV melanoma. INTerpath-001 (NCT05933577) is a double-blind phase 3 randomized controlled trial designed to evaluate the efficacy and safety of adjuvant pembrolizumab plus V940 versus pembrolizumab plus placebo in patients with resected high-risk stage II-IV melanoma. **Methods:** Eligible patients are aged ≥18 years with surgically resected stage IIB or IIC (pathologic or clinical), III, or IV cutaneous melanoma per AJCC 8th ed and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients are ineligible if they have received any prior systemic therapy and if more than 13 weeks has elapsed between last surgical resection and first dose of pembrolizumab. Patients with ocular or mucosal melanoma and past or current in-transit metastases or satellitosis are excluded. All patients must provide a blood sample and a formalin-fixed, paraffin-embedded tumor sample for sequencing. Patients will be stratified by risk (IIB, IIC, IIIA, and IIIB vs IIIC/D and IV) and age (<65 years vs ≥65 years). Approximately 1089 patients will be randomly assigned 2:1 to receive pembrolizumab 400 mg plus V940 1 mg or pembrolizumab 400 mg with placebo. Pembrolizumab will be administered intravenously every 6 weeks and v940 or placebo will be administered intramuscularly every 3 weeks. Treatment will continue for up to 9 doses or until disease recurrence, unacceptable toxicity, or patient withdrawal. The primary end point is RFS by investigator review. Secondary end points are DMFS by investigator review, overall survival, safety and tolerability, and quality of life. Hazard ratios and 95% CIs will be estimated using a stratified Cox regression model with the Efron method of handling ties. Between-treatment differences will be evaluated using a stratified log-rank test. Enrollment is ongoing. Clinical trial information: NCT05933577. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Moderna, Inc., Cambridge, MA, USA.

TPS9617 **Poster Session**

Intralesional administration of L19IL2/L19TNF in high-risk locally advanced basal cell carcinoma or cutaneous squamous cell carcinoma.

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Background: Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) account for 99% of skin neoplasms, with a rising incidence due to increased sun exposure and growing life expectancy. Approximately 0.8-5% of patients (pts) develop high-risk locally advanced (LA) disease, which is treated with surgery, radiotherapy, sonic hedgehog inhibitors, PD1-based immune checkpoint blockade, or chemotherapy. While surgery offers high cure rates, factors such as location, functional and cosmetic impairment, or patient factors including age, comorbidities, and personal preferences may preclude surgery. Intralesional treatment with immunostimulatory drugs represents an attractive therapeutic approach to treat LA BCC and LA cSCC. Here, we investigate a combination of two immunocytokines (Bifikafusp alfa (L19IL2) and Onfekafusp alfa (L19TNF)) targeting the extradomain B of fibronectin (EDB) for the treatment of high-risk locally advanced BCC and cSCC. EDB is an oncofetal antigen that is undetectable in virtually all healthy adult tissues but becomes highly expressed in tumors, including BCC and cSCC. **Methods:** In a single-arm phase II study (NCT04362722), pts with locally advanced, non-metastatic, node-negative, single, or multifocal BCC or cSCC not eligible for surgery or radiotherapy are treated with four weekly intratumoral administrations of L19IL2/L19TNF. The study is divided into two parts: a first exploratory part with a total of 40 pts with laBCC or lacSCC, and a second part where the laBCC cohort has been expanded to up to 72 pts not eligible for surgery or radiotherapy. The first part of the trial has been completed with 28 laBCC pts and 12 lacSCC pts evaluable for safety and efficacy. The pre-specified activity goal for the first stage of accrual was met, and the second stage of accrual began in September 2023, with a total of 39 BCC and 18 cSCC pts enrolled so far. Clinical trial information: NCT04362722. Research Sponsor: Philogen S.p.A.

TPS9618 Poster Session

TRICK-MCC: A proof-of-concept, investigator-initiated study of combination therapy with anti–PD-1, anti–LAG-3, and anti–TIM-3 in participants with advanced or metastatic PD-(L)1 refractory Merkel cell carcinoma.

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Background: Merkel cell carcinoma (MCC) is an aggressive and highly immunogenic skin cancer often associated with the Merkel cell polyomavirus (MCPyV). Immune checkpoint inhibition (ICI) via PD-(L)1 blockade can promote durable responses among patients with metastatic MCC, yet >50% of MCC patients experience disease progression. There is an unmet need for effective treatment options for these patients. One possible strategy to overcome primary and secondary resistance in PD-(L)1 refractory MCC is concurrent targeting of multiple immune checkpoints to facilitate reversal of chronic T cell exhaustion. Based on our preliminary data revealing high expression of PD-1, LAG-3 and TIM-3 on MCC-specific CD8 T cells, which appear to increase upon clinical disease progression in the context of treatment with PD-(L)1 blockade, we hypothesize that concurrent blockade of PD-1, LAG-3 and TIM-3 will overcome immune evasion in patients with PD-(L) refractory MCC. **Methods:** TRICK-MCC (Triple Immune Checkpoint Inhibition in MCC) is an investigator initiated, Phase 2 clinical trial investigating concurrent treatment with anti-PD-1 (retifanlimab), anti-LAG3 (INCAGN02385) and anti-TIM-3 (INCAGN02390) in patients with advanced/metastatic MCC that has progressed after treatment with anti-PD-(L)1. Target enrollment is 20 patients total, with 5 patients enrolled as of Jan 2024. Patients will receive anti-PD-1 q4w and anti-TIM-3 and LAG-3 q2w for up to 24 weeks (Induction Phase) followed by all drugs q6w (Maintenance Phase). Treatment will end 2 years after starting the study drugs, or upon disease progression, unacceptable toxicity, or study withdrawal. Primary objective is objective response rate (ORR). Secondary objectives are duration of response, progression free survival, overall survival, and incidence and severity of adverse events. Interim analysis will be done after 10 patients have been enrolled and followed sufficiently long to assess ORR. An observed ORR of 25%will be considered as clinically meaningful in this population with no reliable standard treatments. Serial tumor biopsies and blood samples will be obtained in all patients, unless deemed unsafe or not feasible. Planned correlative studies aim to better characterize the prevalence and significance of cancer-specific T cell exhaustion (through rigorous study of MCPyV-specific T cells), the immunologic effects of triple ICI, and alternative mechanisms of PD-(L)1 resistance beyond T cell exhaustion in PD-(L)1 resistant tumors. We hope to gain insights that are broadly applicable to solid tumor immunotherapy. Clinical trial information: NCT06056895. Research Sponsor: None.

TPS9619 Poster Session

A phase 2, open-label, 2-cohort study to evaluate patient preference for nivolumab (NIVO) + relatlimab (RELA) fixed-dose combination (FDC) subcutaneous (SC) vs NIVO + RELA FDC intravenous (IV) and NIVO SC vs NIVO IV in participants with melanoma.

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Background: The oncology burden on healthcare resources and patients increases as the number of individuals with cancer grows, necessitating treatment options offering improved convenience to patients. SC delivery of monoclonal antibodies in various cancer indications has previously been shown to be effective, well tolerated, and preferred by patients over IV infusion. In CheckMate 67T (NCT04810078), noninferiority of exposure (time-averaged serum concentration at Day 28 and trough serum concentration at steady state) and efficacy (objective response rate by BICR) were previously reported for NIVO SC 1200 mg + recombinant human hyaluronidase PH20 (rHuPH20) vs IV in patients with locally advanced/metastatic clear cell renal cell carcinoma. RELATIVITY-127 (NCT05625399) is ongoing to establish exposure noninferiority of NIVO + RELA + rHuPH20 FDC SC to IV in patients with previously untreated metastatic/unresectable melanoma. This phase 2, open-label study CA224-1044 (NCT06101134) assesses patient preference for NIVO SC or NIVO + RELA FDC SC vs IV formulations after transitioning from IV to SC in patients with melanoma and aims to further characterize the safety profile of immuno-oncology therapy during IV-to-SC switch. **Methods:** Cohort 1 includes adult patients with previously untreated stage III (unresectable) or stage IV (metastatic) melanoma who will receive NIVO + RELA FDC IV every 4 weeks (Q4W) for 2 cycles (28-day cycle) followed by NIVO + RELA + rHuPH20 FDC SC Q4W until disease progression, unacceptable toxicity, or a maximum total treatment duration of 2 years, whichever comes first. Cohort 2 includes adult patients with completely resected stage IIB/C, stage III or stage IV melanoma who will receive NIVO IV Q4W for 2 cycles (28-day cycle) followed by NIVO SC + rHuPH20 Q4W until disease recurrence, unacceptable toxicity, or a maximum total treatment duration of 1 year, whichever comes first. The primary endpoint is the proportion of participants preferring the SC route of administration based on question 7 of the Patient Experience and Preference Questionnaire after the Cycle 4 Day 1 dose. This question evaluates patient preference for IV or SC or no preference in treatment administration and was previously used in CheckMate 8KX. Secondary endpoints include safety outcomes such as adverse events (AEs), serious AEs, treatment-related AEs, AEs leading to discontinuation, immune-mediated AEs, other events of special interest, injection/infusion-related AEs, deaths, and laboratory abnormalities. Safety is assessed for IV period, SC period (8 weeks each) and overall study period. Exploratory endpoints include additional measures of patient experience and preference for IV vs SC. The study is recruiting to enroll 50 patients per cohort. Clinical trial information: NCT06101134. Research Sponsor: Bristol Myers Squibb.

TPS9620 Poster Session

INTASYL PH-762: PD-1 intratumoral immunotherapy for cutaneous carcinoma.

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Background: Immune checkpoint-targeted antibodies directed at PD-1 or PD-L1 block co-inhibitory receptors expressed by anti-tumor T cells, breaking immune tolerance against tumor cells and generating cancer immunity. Intratumoral (IT) immunotherapy aims to use the tumor as a 'self-vaccine'. Local immune stimulation may induce robust priming of an anti-tumor immune response and generate abscopal tumor responses, mediated by circulating activated anti-tumor immune cells. Local delivery of immunotherapy minimizes systemic exposure and off-target toxicities and may decrease tumor size and improve surgical morbidity. PH-762 is an INTASYL compound designed to precisely silence PD-1 mRNA. INTASYL is a patented, self-delivering RNAi technology platform designed to impart specific properties to small interfering RNAs. PH-762's unique structural and chemical modifications ensure an optimized cell and tissue uptake profile with IT administration. In vitro investigations have demonstrated efficient uptake of PH-762 by human T cells, silencing of PD-1 mRNA and subsequent protein reduction. Preclinical studies have shown that IT injections of murine-targeted PH-762 (mPH-762) can silence PD-1 mRNA in T cells within the tumor and increase the secretion of IFN-γ. mPH-762 was well tolerated at the maximum administered dose and treatment with mPH-762 provided robust and statistically significant inhibition of tumor growth. Toxicokinetic studies conducted in marmoset monkeys demonstrated that PH-762, when administered intravenously at doses of up to 147 mg/kg, is well-tolerated. No cytokine-release associated cytokines were detected in the plasma of treated monkeys at this dose. **Methods:** This open-label Phase 1 clinical study (NCT 06014086) is designed to evaluate the safety and tolerability of neoadjuvant use of IT PH-762 in cutaneous squamous cell carcinoma, melanoma, or Merkel cell carcinoma, to determine the pharmacokinetic profile of PH-762 after IT injection, to observe pathologic and immunologic tumor responses, and to determine the recommended dose for development. Escalating dose concentrations of PH-762 (from 1.14 mg/mL through 22.00 mg/mL) are tested serially in cohorts of 3 patients each. Patients receive IT PH-762 once weekly, 4 times over a 3-week period prior to surgical excision, which occurs 5 weeks after the initial injection. Following excision of the tumor, patients are followed for approximately 11 weeks. Tumor changes are evaluated per iRECIST criteria and pathological response. Immunological response in tumor tissue and blood samples are assessed as secondary endpoints. This clinical study, enrolling patients since November 2023, will establish the basis for continued clinical development of PH-762. Clinical trial information: 06014086. Research Sponsor: None.