LBA9500 **Oral Abstract Session**

Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: The phase 3 KEYNOTE-716 study.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*. Research Sponsor: Merck & Co., Inc., Kenilworth, NJ, USA.

9501 **Oral Abstract Session**

Survival data of PRADO: A phase 2 study of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma.

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Background: In the OpACIN-neo study, 2 cycles neoadjuvant (neoadj) IPI 1mg/kg + NIVO 3mg/kg (I1N3) have been identified as most favorable dosing scheme with a pathologic response rate (pRR) of 77% and 20% grade 3-4 irAEs. After 24.6 months median follow-up (FU), the 2-year (2y) RFS was 96.9% for patients (pts) with pathologic response versus 35.5% for non-responders (>50% viable tumor; pNR). These data raised the question whether therapeutic lymph node dissection (TLND) could be safely omitted in pts achieving a major pathologic response (MPR; ≤10% viable tumor) in their index node (ILN; largest LN metastasis at baseline), and if additional adjuvant (adj) therapy could improve the outcome of pNR pts. **Methods:** PRADO is an extension cohort of the phase 2 OpACIN-neo study aiming to confirm the pRR and safety of neoadj I1N3 and to test response-driven subsequent therapy. Pts with stage III melanoma were included to receive 2 cycles neoadj I1N3 after marker placement in the ILN. ILN resection was planned at week 6. Pts that achieved MPR in the ILN did not undergo TLND; pts with partial response (pPR; >10 – ≤50% viable tumor) underwent TLND; and pts with pNR underwent TLND and received adj NIVO or dabrafenib plus trametinib (D+T) for 52 weeks ±radiotherapy (RT). Primary endpoints were pRR in the ILN and RFS at 2y. The 2y RFS rates were calculated using a Kaplan Meier based method. **Results:** Between Nov 2018 and Jan 2020, 99 patients were enrolled and treated with at least 1 cycle of neoadj I1N3. We previously showed a pRR of 72% (95% CI 62 - 80), including 60 (61%) pts with MPR and 11 (11%) pts with pPR. TLND omission in MPR pts resulted in significant reduced surgical morbidity and improved quality of life. There were 27 non-responders of whom 6 developed distant metastasis before ILN resection. Of the other 21 pNR pts, 7 received adj NIVO, 10 adj D+T, 3 no adj therapy, and 1 was lost to FU. After a median FU of 27.9 months (data cutoff Jan 31, 2022), the estimated 2y RFS rate for MPR pts was 93.3% (95% CI 87.2 – 99.9), with 4/60 pts developing a regional relapse. Distant metastasis-free survival (DMFS) was 100%. Of the 11 pPR pts, 4 developed a relapse (all distant), resulting in a 2y RFS and DMFS rate of 63.6% (95% CI 40.7 – 99.5). The 2y RFS rate of the pNR pts was 71.4% (95% CI 54.5 – 93.6), and DMFS 76.2%. At data cutoff, relapse occurred in 2/7 pNR pts with adj NIVO and 3/10 with adj D+T. Final data cutoff is planned mid Feb, 2022. **Conclusions:** MPR pts in whom TLND was omitted showed a 2y RFS rate of 93.3% and DMFS of 100%, indicating that the ILN procedure and omitting adj therapy could become a safe approach in these pts. Adj systemic therapy in pNR pts seems to improve RFS as compared to historic control (OpACIN-neo), thus should be considered in this unfavorable pNR group. The DMFS rate of 63.6% observed in the pPR group advocates the consideration of adj therapy also for this subgroup in the future. Clinical trial information: NCT02977052. Research Sponsor: BMS.

9502 **Oral Abstract Session**

Neoadjuvant PD-1 blockade in patients with resectable desmoplastic melanoma (SWOG 1512).

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Background: Desmoplastic melanoma (DM) is a rare cancer defined by a dense fibrous collagen matrix. It is associated with high UV exposure leading to a high mutational load. When locally advanced, the standard of care is wide excision and radiation therapy due to its propensity for local relapses. Metastatic DM has a high response rate (RR) to PD-1 blockade therapy (Eroglu et al. Nature 2018). We hypothesized that neoadjuvant treatment with anti-PD-1 monotherapy may induce pathologically confirmed regressions in a high percentage of cases, potentially allowing for less extensive local treatment. **Methods:** Patients > 18 years old with histologically confirmed resectable (primary, recurrent, or regional lymph node metastasis) DM with clinical evidence of residual disease received pembrolizumab 200 mg q3 weeks (wk) 3 followed by excision. No adjuvant therapy was administered. Primary endpoint: pathological complete response (pCR), with the assumption that pCR of 25% would be considered a positive result worthy of future study. To test this hypothesis, a single arm trial with 25 eligible patients would have a 3.4% probability of a positive result with a true pCR of 5%, and a power of 90% of a positive result if the true pCR is 25%. Secondary endpoints: clinical RR by imaging and clinical exam, median overall survival (OS), and evaluation of safety/tolerability of neoadjuvant pembrolizumab. Adverse events were assessed q3 wk. Disease assessments occurred at baseline and q9 wk. NCT02775851. **Results:** We enrolled-29 eligible patients with resectable DM. One patient refused treatment and was omitted from further analysis. Median age was 75, 79% were male, primary sites of disease were 72% H&N, 10% torso, 14% extremities, 3% unknown. No patients received prior systemic therapy. Mean time from C1D1 treatment to surgery was 84.2 (range: 52-135) days, mean number of cycles received 3.3 (range: 2-4). 26/27 (93%) of patients underwent wide excision of the resectable disease, of which 14 (54%) underwent sentinel lymph node biopsy. One patient underwent resection of a nodal recurrence thus did not require wide excision. pCR was noted in 15/27 (56%) of patients (95% CI: 35%-75%). One patient without a pCR had a major pathologic response with 0.2 mm residual melanoma. In addition, one patient with a clinical CR did not undergo resection by choice. None became inoperable. Clinical RR was 52% (95% CI: 32%-71%). Median OS has not been reached, with two nontreatment related deaths (acute hypoxic respiratory failure; unknown). No > grade 2 related adverse events were observed. **Conclusions:** Neoadjuvant pembrolizumab in resectable DM results in a high pCR rate with excellent tolerance, which supports consideration of PD-1 blockade therapy prior to surgery. Funding: U10CA180888 and U10CA180819; and in part by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Clinical trial information: NCT02775851. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

9503 **Oral Abstract Session**

NeoTrio: Randomized trial of neoadjuvant (NAT) pembrolizumab (Pembro) alone, in sequence (SEQ) with, or concurrent (CON) with dabrafenib plus trametinib (D+T) in resectable BRAF-mutant stage III melanoma to determine optimal combination of therapy.

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Background: Combination anti-PD(L)1 and BRAF/MEK-targeted therapy (TT) improves PFS in stage IV melanoma vs TT. In stage IV melanoma recent data suggest immunotherapy 1st until progression, rather than BRAF-TT, improves OS, and induction TT upfront adds little benefit. NeoTrio explored the optimal combination of BRAF-TT and anti-PD1 using the NAT platform in pts with stage III melanoma (NCT02858921). **Methods:** 60 pts with resectable, RECIST measurable stage III (no in-transit) $BRAF^{V600}$-mutant melanoma were randomized 1:1:1 to 3 arms of 6 wks of NAT followed by complete lymph node dissection (CLND): A) Pembro ALONE (200mg Q3W x 2); B) SEQ - D+T (150mg bd + 2mg od) for 1 wk followed by pembro (200mg x 2); C) CON – D+T+pembro (doses as SEQ). Pts had 46 wks pembro post-CLND. Primary endpoint was the pathological response rate (pRR) and pathological complete response (pCR) at wk 6. Secondary endpoints; RECIST RR at wk 6, event-free survival (EFS), RFS, OS, adverse events (AE) and translational endpoints. **Results:** At data cutoff 2 Jan 2022, 20 pts per arm had similar baseline characteristics; overall 42% female, med age 53 yrs, 82% BRAF V600E, 62% clinical N1b. Med f/u was 20 months (95% CI 17-31). The pCR rate and pRR were highest in CON arm, and similar in ALONE and SEQ arms (Table). Events (progression before surgery, recurrence after surgery or death) were highest in ALONE arm at this 1st analysis (Table). Assessment of the durability of path response subtypes in each arm is ongoing. Most common Rx related AE were fatigue (65%, 70%, 70%, ALONE, SEQ and CON respectively), pyrexia (0%, 25%, 85%) and rash (50%, 35%, 35%). Gd 3/4 AE occurred in 30%, 25% and 55%, respectively; pyrexia and hepatitis were common in CON during NAT. Rx interruptions during NAT occurred in 0, 3 and 19 pts, respectively; 1, 0 and 8 pts permanently discontinued. Post NAT surgical operability was the same or improved in 81%. Longitudinal analysis of melanoma tissue, microenvironment and microbiome is ongoing. **Conclusions:** CON D+T+pembro achieved the highest pRR, pCR rate, but with greater toxicity. Recurrences were seen in those with pCR/near pCR in BRAF-TT containing arms, but not in pembro ALONE, in keeping with previous data of NAT with checkpoint inhibitors vs BRAF-TT. Short course of D+T prior to PD1 did not improve path response, despite previous translational data showing increased tumour infiltrating T-cells early-during treatment with D+T. Follow up is ongoing. Clinical trial information: NCT02858921. Research Sponsor: Melanoma Institute Australia and MSD.

	ALONE (n=20)	SEQ (n=20)	CON (n=20)
pRR	11 (55%)	10 (50%)	16 (80%)
pCR	6	4	10
Near-pCR	2	2	1
pPR	3	4	5
pNR	7	10	3
RECIST ORR/CR	60% / 10%	45% / 0%	70% / 30%
No. Events	7*	6	4¨
No. Recurred by pCR/near-pCR/pPR/pNR	0/0/2/3	0/1/0/5	1/0/2/0
No. Death	3	1	2
1-yr EFS (95% CI)	80% (64-100)	80% (64-100)	79% (62-100)

*2 pts and ¨1 pt progressed prior to surgery; no CLND was performed.

9505 **Oral Abstract Session**

Nivolumab (NIVO) + relatlimab (RELA) versus NIVO in previously untreated metastatic or unresectable melanoma: OS and ORR by key subgroups from RELATIVITY-047.

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Background: In the phase 2/3 RELATIVITY-047 trial, NIVO + RELA as a fixed-dose combination (FDC) significantly improved the primary endpoint of progression-free survival (PFS) versus NIVO in patients (pts) with previously untreated metastatic or unresectable melanoma. Secondary endpoints showed a clinically meaningful improvement in overall survival (OS), although not statistically significant, and a higher objective response rate (ORR). As previously reported, PFS and OS favored NIVO + RELA over NIVO across prespecified stratification factors (LAG-3 expression, PD-L1 expression, *BRAF* V600 mutation status, and metastasis stage). Here we report the first disclosure of ORR analyzed by prespecified stratification factors and OS and ORR in additional subgroups. **Methods:** Pts were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg FDC or NIVO 480 mg intravenously Q4W. The primary endpoint was PFS per RECIST v1.1 assessed by blinded independent central review (BICR). Secondary endpoints were OS and ORR by BICR, tested in hierarchy. Exploratory analyses were performed for PFS, OS, and ORR by prespecified subgroups. **Results:** PFS continued to favor NIVO + RELA over NIVO across key subgroups. OS and ORR also favored NIVO + RELA over NIVO across key subgroups including those associated with poor prognosis (Table). ORR favored NIVO + RELA over NIVO for pts with LAG-3 expression ≥ 1% (47% vs 35%) and < 1% (31% vs 24%), PD-L1 expression ≥ 1% (53% vs 45%) and < 1% (36% vs 24%), and *BRAF* wild-type (43% vs 34%) and mutant (43% vs 31%) melanoma, respectively. Additional key prespecified subgroups will be presented. In all treated pts, NIVO + RELA maintained a manageable safety profile with no new or unexpected safety signals. **Conclusions:** NIVO + RELA was favored over NIVO across key subgroups for PFS, OS, and ORR, and findings appeared consistent with outcomes in the overall population. NIVO + RELA had a favorable benefit-risk profile. Clinical trial information: NCT03470922. Research Sponsor: Bristol Myers Squibb.

	Patients, n		mOS, months (95% CI)			ORR, % (95% exact CI)	
Subgroup	N+R	N	N+R	N	Unstratified HR (95% CI)	N+R	N
Overall	355	359	NR	34 (25.2–NR)	0.81[‡] (0.64–1.01)	43 (37.9–48.4)	33 (27.8–37.7)
Metastasis stage M1c*	151	127	34 (17.9–NR)	22 (13.8–33.2)	0.78 (0.56–1.08)	37 (29.4–45.3)	29 (21.4–37.9)
High tumor burden (≥ Q3)[†]	84	75	17 (10.8–34.0)	9 (6.2–19.1)	0.75 (0.51–1.11)	32 (22.4–43.2)	23 (13.8–33.8)
LDH ≤ ULN	225	231	NR	NR	0.76 (0.55–1.06)	50 (43.1–56.5)	35 (28.5–41.2)
LDH > ULN	129	128	17 (10.8–31.5)	14 (9.7–21.0)	0.81 (0.59–1.11)	32 (23.9–40.6)	29 (21.2–37.6)

CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; mOS, median overall survival; NR, not reached; N, nivolumab; N+R, nivolumab plus relatlimab; n, number of patients; Q3, quartile 3; R, relatlimab; ULN, upper limit of normal. *AJCC v8; [†]Tumor burden quartile as determined by BICR at baseline; [‡]Unstratified HR was 0.81 and stratified HR was 0.80.

9506 **Oral Abstract Session**

Navtemadlin (KRT-232) activity after failure of anti-PD-1/L1 therapy in patients (pts) with *TP53*^{WT} Merkel cell carcinoma (MCC).

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Background: MCC is a rare, aggressive, neuroendocrine skin cancer with a high risk of recurrence and metastases. A median survival of about 4 mo for pts with metastatic MCC who failed anti-PD-1/L1 therapy highlights an urgent need for novel therapies. In *TP53*^{WT} MCC, oncoproteins from the Merkel cell polyomavirus (MCPyV) inhibit p53 tumor suppressor functions by activating murine double minute 2 (MDM2). Navtemadlin is a potent, selective, orally available MDM2 inhibitor that overcomes MDM2 dysregulation by restoring p53 activity and inducing apoptosis of *TP53*^{WT} tumors. **Methods:** The dose-finding, phase 1b/2 KRT-232-103 study (NCT03787602) evaluated navtemadlin in adult *TP53*^{WT} MCC pts who failed anti-PD-1/L1 therapy. Pts were randomly assigned to oral navtemadlin once daily in 21- or 28-day cycles: 240 mg 7 days (D) on/14D off or 5D on/23D off, 180 mg 5D on/23 D off or 7D on/21D off, or 120 mg 7D on/14D off, until disease progression or unacceptable toxicity. The primary endpoint was Recommended Phase 2 Dose (RP2D); objective response rate (ORR) was assessed per RECIST v1.1. **Results:** As of Nov 30, 2021, 31 pts were enrolled with median age 66 y (range, 25-82); 52% had visceral disease and 71% had received ≥2 lines of prior therapy. Baseline tumor profiling of available samples showed low tumor mutation burden, MCPyV-positivity, and nonamplified *MDM2* gene in 100%, 92%, and 100% of pts, respectively. Treatment-emergent adverse events (TEAEs) were observed in 100% (68% grade 3/4) of pts. The most common Grade 3/4 TEAEs were hematologic: 32% anemia, 32% lymphopenia, and 19% thrombocytopenia. Navtemadlin doses ≤180 mg were well tolerated with fewer dose reductions and longer treatment durations; subsequently the 240 mg arms were closed to further enrollment. Evaluable pts receiving 180 mg 5D on/23D off showed a 25% confirmed ORR, a 38% unconfirmed + confirmed ORR, and a 63% disease control rate (Table); median duration of response was not reached (range, 6-16.2+ mo) and median time to treatment response was 4.1 mo (range, 1.2-7). Notably, one responder, following a prolonged partial response, achieved complete metabolic remission by PET/CT after 2 y on treatment. The 120 mg arm was closed due to a low response rate. The 180 mg dose has been selected for further evaluation. **Conclusions:** Navtemadlin is the first targeted agent to show promising single-agent activity in heavily pretreated MCC pts who failed anti-PD-1/L1 therapy. This study demonstrates that upregulation of the p53 pathway is a viable therapeutic strategy in MCC. Clinical trial information: NCT03787602. Research Sponsor: Kartos Therapeutics, Inc.

Navtemadlin activity in evaluable* MCC Pts (n=29).

n (%)	240 mg 7D on/ 14D off (n=6)	240 mg 5D on/ 23D off (n=7)	180 mg 5D on/ 23D off (n=8)	180 mg 7D on/ 23D off (n=1)	120 mg 7D on/ 14D off (n=7)
Confirmed ORR	1 (17)	1 (14)	2 (25)	0	1 (14)
Unconfirmed + confirmed ORR	2 (33)	1 (14)	3 (38)	0	1 (14)
Disease control rate	2 (33)	2 (29)	5 (63)	0	1 (14)

*Pts who have ended treatment or been on treatment for >10 wk.

9507 **Oral Abstract Session**

Nivolumab (NIVO) + tacrolimus (TACRO) + prednisone (PRED) +/- ipilimumab (IPI) for kidney transplant recipients (KTR) with advanced cutaneous cancers.

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Background: Cancer is a leading cause of death among KTR, but these patients (pts) have been excluded from trials of immune checkpoint inhibitors due to immunosuppression and risk of allograft loss. We report findings from the first prospective clinical trial of NIVO + TACRO + PRED +/- IPI in KTR with selected advanced cutaneous cancers. **Methods:** The primary composite endpoint was lack of tumor progression per RECIST v1.1 without allograft loss at 16 weeks (W) on NIVO. Adult KTR with advanced melanoma, basal, cutaneous squamous, or Merkel cell carcinoma (MEL, BCC, CSCC, MCC), for whom non-immune therapies were insufficient were eligible. Immunosuppression was standardized to low-dose TACRO (goal trough 2-5 ng/mL) + PRED 5mg daily; pts then received NIVO 480mg IV q4W. Pts with progressive disease (PD) could receive NIVO 3mg/kg + IPI 1mg/kg IV q3W x 4 followed by NIVO 480mg IV q4W. Donor-derived cell-free DNA (dd-cfDNA) levels were measured q2W as a potential predictor of allograft rejection. **Results:** From 11/2019 - 4/2021, of 12 pts enrolled, 8 pts with CSCC, MCC or MEL were evaluable for response (Table). All pts experienced PD on NIVO; treatment-related allograft loss (TRAL) occurred in 1 pt. 6 pts then received IPI + NIVO. Responses: 2 (33%) with marked tumor regression at 6W and eventual complete response (CR; 1 with TRAL), and 4 (67%) with PD (1 with TRAL). 7/8 pre-NIVO tumor biopsies contained a paucity of infiltrating immune cells. Only 2/5 on-NIVO biopsies demonstrated moderate immune infiltrates; both of these pts later developed a CR to IPI + NIVO. Rejecting allografts contained dense immune responses (plasma cells, CD4+ & CD8+ lymphocytes, PD-1+ lymphocytes, macrophages, PD-L1+ glomerular endothelium, and focal PD-1 & PD-L1 positivity in renal tubules). In 2/3 pts with TRAL, elevations in dd-cfDNA levels occurred 10 and 15 days earlier than increases in weekly serum creatinine levels. TRAL #3 occurred after discontinuation of study therapy (including TACRO) and dd-cfDNA monitoring. **Conclusions:** In KTR receiving low-dose TACRO + PRED, NIVO augments tumor immune cell infiltration in some pts but is insufficient to mediate tumor regression. Adding IPI can enhance anti-tumor immunity and mediate tumor regression. TACRO + PRED was insufficient to prevent allograft rejection after PD-1 +/- CTLA-4 blockade in 2/8 pts. In pts with TRAL, increased dd-cfDNA levels preceded increased serum creatinine. Based on these findings, we are modifying the trial therapy regimen to augment anti-tumor immunity and preserve allograft function. Clinical trial information: NCT03816332. Research Sponsor: U.S. National Institutes of Health, The Marilyn and Michael Glosserman Fund for Basal Cell Carcinoma and Melanoma Research, and The Bloomberg~Kimmel Institute for Cancer Immunotherapy.

		CD8+ Immunohistochemistry (0-3= none, mild, moderate & severe; *no specimen available)			NIVO		IPI+NIVO	
Pt ID	Diagnosis	Pre-NIVO	On-NIVO	On-IPI/NIVO	Tumor response	Allograft loss	Tumor response	Allograft loss
1	MCC	1	1	*	PD	N	PD	N
2	CSCC	1	2	3	PD	N	CR	N
3	MCC	1	0	0	PD	N	PD	Y
4	CSCC	1	*	*	PD	N	PD	N
5	CSCC	1	*	N/A	PD	N	N/A	N/A
6	CSCC	3	2	*	PD	N	CR	Y
7	MEL	1	1	*	PD	Y	PD	N
8	CSCC	1	*	N/A	PD	N	N/A	N/A

9508 **Oral Abstract Session**

A phase II clinical trial of camrelizumab (CAM, an IgG4 antibody against PD-1) combined with apatinib (APA, a VEGFR-2 tyrosine kinase inhibitor) and temozolomide (TMZ) as the first-line treatment for patients (pts) with advanced acral melanoma (AM).

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Background: PD-1 monotherapy as the first line stand treatment for advanced melanoma yields an objective response rate (ORR) of < 20% in AM. Although multiple clinical trials are ongoing testing TMZ/APA, TMZ/PD-1 and APA/PD-1 combo therapies in AM, the reported ORR (range 17-23.8%) are far from satisfactory. We therefore conducted a phase II study of CAM/APA/TMZ combo in this subtype aiming for improved efficacy. **Methods:** We performed a single center, single arm phase II study (NCT04397770) testing the efficacy and safety of CAM/APA/TMZ combo as first-line therapy in pts with advanced AM. The primary endpoint was ORR per RECIST1.1, secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. All pts received iv CAM (200mg q2w), iv TMZ (200mg/m2 d1-5, q4w) and po APA (250mg qd) until disease progression or intolerable toxicity. **Results:** By Jan 2022, fifty pts were enrolled (48 evaluable), the median follow-up was 12.1 mo (IQR 8.4-14.5). Thirty-one pts achieved CR/PR as the best response (including 1 CR and 30 PR), the ORR was 64.6% (95% CI 49.4-77.4%). The DCR was 95.8% (95%CI, 84.6-99.3%). Both the median PFS and OS was not reached (NR); 6-mo and 12-mo PFS rate was 81.7% (95%CI 71.6-93.3%) and 62.9% (95%CI 48.4-81.7%), respectively; 12-mo OS rate was 82.3% (95%CI 68.2-99.2%). The incidence of treatment-related adverse events (TRAEs) was 94% (47/50). Of 50 patients, the most common grade ≥3 TRAEs included γ-glutamyl transferase elevation (24.0%), direct bilirubin elevation (22.0%), aspartase transaminase elevation (20.0%), alanine transaminase elevation (16.0%), and hypertriglyceridemia (14.0%). No treatment-related deaths occurred. **Conclusions:** The CAM/APA/TMZ combination demonstrated promising efficacy as the first-line treatment for pts with advanced AM, and was generally well tolerated. Phase III randomized control trial is warranted. Clinical trial information: NCT04397770. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

LBA9509 **Poster Discussion Session**

Isolated hepatic perfusion as a treatment for uveal melanoma liver metastases, first results from a phase III randomized controlled multicenter trial (the SCANDIUM trial).

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2022, issue of the *Journal of Clinical Oncology*. Research Sponsor: Assar Gabrielsson Foundation and Gothenburg Medical Association.

9510 **Poster Discussion Session**

FOCUS phase 3 trial results: Percutaneous hepatic perfusion (PHP) with melphalan for patients with ocular melanoma liver metastases (PHP-OCM-301/301A).

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Background: Ocular melanoma, the most common intraocular malignancy, frequently metastasizes to the liver but to date there is no established standard of care for hepatic-dominant ocular melanoma patients. The FOCUS trial began as a randomized, Ph 3 trial (301) comparing PHP with best alternative care (BAC). The trial was subsequently amended (301A) to halt the BAC arm due to enrollment concerns. **Methods:** Eligible patients with hepatic-dominant ocular melanoma were randomized 1:1 to receive PHP or BAC (investigator's choice of TACE, pembrolizumab, ipilimumab, or dacarbazine) on the 301 trial. All eligible patients received PHP on the 301A trial. PHP patients could receive up to 6 PHP treatments, repeated every 6-8 weeks with melphalan dosed at 3.0mg/kg ideal body weight (IBW). Patients with progressive disease (PD) were discontinued from study treatment and all patients are followed until death. Patientswere imaged every 12 (±2) weeks until PD. The primary endpoint, ORR (per RECIST 1.1) as assessed by Independent Review Committee, was characterized by the point estimate and 95% CI for each group (PHP and BAC). **Results:** 144 patients were enrolled overall; 102 were assigned to PHP (301: n = 43; 301A: n = 59) and 42 were assigned to BAC. 91 PHP patients received treatment (301: n = 40; 301A: n = 51) and 32 BAC patients received treatment. ORR among PHP patients was 35.2% (32/91; 95% CI: 25.44-45.88%). ORR among BAC patients was 12.5% (4/32; 95% CI: 3.51-28.99%; p= 0.0154). The median DOR was 14 months for PHP patients and not calculable for BAC patients. The DCR among PHP patients was 73.6% (67/91; 95% CI: 63.35-82.31%) and among BAC patients was 37.5% (12/32; 95% CI: 21.10-56.31%; p= 0.0002). The median PFS was 9.03 months (95% CI: 6.34-11.56) among PHP patients and was 3.12 months (95% CI: 2.89-5.65) among BAC patients (p= 0.0007). The median OS was 20.53 months (95% CI: 16.59-24.35) among PHP patients and was 14.06 months (95% CI: 9.99-19.78) among BAC patients. With the last treatment occurring in May 2021, the OS, DOR, and PFS data continues to mature as patients are still being followed for survival. Among the 94 patients assessed for safety after treatment with PHP, 42.6% of patients experienced a serious treatment-emergent adverse event, the majority of which were hematological, transient in nature, and resolved without sequelae. There were no treatment related deaths in the trial. **Conclusions:** In this analysis of data from the FOCUS trial, PHP demonstrates superior ORR, DOR, DCR, PFS, and OS in comparison with BAC in the treatment of hepatic metastases from ocular melanoma. This therapy offers a potential option for patients with this rare indication that is associated with a poor prognosis and few treatment options. Clinical trial information: NCT02678572. Research Sponsor: Delcath Systems, Inc.

9511 **Poster Discussion Session**

First interim analysis of the SirTac trial: A randomized phase II study of SIRT and DSM-TACE in patients with liver metastases from uveal melanoma.

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Background: The liver is the most common site of metastases in patients (pts) with uveal melanoma (UM). Here, we present results from the prespecified first interim analysis of the SirTac trial, a prospective, single-center, randomized, investigator-initiated, open-label phase 2 study of Selective Internal Radiation Therapy with Yttrium-90-bearing resin microspheres; SIR-Spheres (SIRT) vs Transarterial Chemoembolization with Cisplatin and degradable starch microspheres; EmboCept S (DSM-TACE) in pts with liver-dominant metastatic UM. **Methods:** Pts with histologically confirmed, liver-dominant metastatic UM and ECOG PS 0-2 were enrolled and randomized 1:1 to SIRT or DSM-TACE. Randomization was stratified by lactate dehydrogenase (<2x vs ≥2x upper limit of normal) and pre-treatment with antiangiogenic agents. Extrahepatic metastases were allowed, if asymptomatic. Primary endpoint was progression-free survival (PFS). A total of 108 pts (54 per arm) were planned to be enrolled. Pts received TACE every 4-6 weeks until tumor devascularization or disease progression or intolerable toxicity was observed, and SIRT either as one whole-liver application or in two sequential sessions for each liver lobe. The primary objective of this prespecified analysis was to assess response by RECIST criteria v1.1 in the per-protocol (PP) population of the first 40 pts (20 pts in each arm). **Results:** Two patients had been treated with previous liver surgery, whereas all other patients had not received previous treatment for metastatic disease. There were no clinicopathological differences between the groups, except for a difference in age (median age SIRT arm 64 y vs 75 y in the TACE arm, p=0.018). All but 1 pt received treatment as randomized. This pt was excluded and replaced by the next TACE pt for this PP interim analysis. There were no differences in best overall response rates between the groups (no complete response, 1 partial response in both arms, stable disease in 19 (95%) and 17 (85%) pts in the SIRT and TACE arm, respectively, and 2 pts with progressive disease in the TACE arm). At a median follow-up of 13.9 mo from treatment start, median PFS in the PP population was 4.9 mo in the SIRT arm vs 2.2 mo in the TACE arm (p=0.037), with a higher median liver-PFS in the SIRT vs TACE arm (8.3 vs 2.2, p=0.026). **Conclusions:** In this planned interim analysis treatment in both arms was feasible with no differences in response. The explorativePFS analysis allows no conclusions on the final outcome after completion of the trial. The study continues recruitment. Clinical trial information: NCT02936388. Research Sponsor: Sirtex Medical, PharmaCept GmbH, Other Foundation.

9512 **Poster Discussion Session**

Toripalimab plus axitinib versus toripalimab or axitinib alone in patients with treatment-naive unresectable or metastatic mucosal melanoma: Interim results from a randomized, controlled, phase II trial.

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Background: A phase IB trial had showen promising antitumor activity with toripalimab (T, a PD-1 antibody) plus axitinib (A, a VEGF receptor inhibitor) in treatment-naive unresectable or metastatic mucosal melanoma. Now we conducted a phase II trial to compare the combined treatment with monotherapy. **Methods:** In this randomized, controlled, phase II trial, patients with pathologically confirmed treatment-naive unresectable or metastatic mucosal melanoma were stratified by PD-L1 expression and randomized 1:1:1 into three groups to receive treatment of T+A (toripalimab 240 mg i.v. every 3 weeks, axitinib 5 mg orally twice a day), T (toripalimab 240 mg i.v. every 3 weeks) or A (axitinib 5 mg orally twice a day). Subjects in T or A who meet the criteria after disease progression may cross over to receive T+A. The primary endpoint was progression-free survival (PFS). Secondary endpoints included Objective response rate (ORR), Duration of response (DOR), overall survival (OS), and safety. The protocol was registered at ClinicalTrials.gov (NCT03941795). This is the interim analysis for efficacy and safety. **Results:** Between Nov 2019 and Jan 2022, 51 patients were randomized (18 to T+A, 20 to T, and 13 to A due to preliminary efficacy analysis). Anatomic site of head and neck, gastrointestinal, gynecological were 49.0%, 29.4%, 21.6%, respectively. Stage II or III unresectable, M1a, M1b, M1c were 3.9%, 23.5%, 17.6%, 51.0%, respectively. PD-L1 positivity was defined as ≥1% of tumor cells and/or infiltrating immune cells and were identified in 55.6%, 45.0%, 53.8% patients in T+A, T, A group, respectively. 17, 17 and 12 patients could be evaluated in T+A, T and A group, respectively. 24 patients from T or A crossover to T+A group. At a median follow-up of 6.60 months, patients receiving T+A had a higher median PFS (5.83 vs 2.80 vs 1.40 months; HR = 0.538; 95% CI, 0.237 to 1.221; HR = 0.444; 95% CI, 0.182 to 1.081; P = 0.170), ORR (35.3% (29.7% if including crossover patients) vs 17.6% vs 8.3%), DOR (82.4% (70.3% if including crossover patients) vs 52.9% vs 58.3%) versus T or A group. The median OS was not reached. 80.4% patients experienced treatment-related adverse events (TRAEs). The most common TRAEs were mild (grade 1 or 2) and included diarrhea, proteinuria, hand and foot syndrome, fatigue, elevated transaminase, elevated bilirubin, hypertension, hypo- or hyperthyroidism, and rash. Grade 3 or greater TRAEs occurred in 33.3%, 30.0%, 30.8% of patients in T+A, T, A groups. **Conclusions:** Toripalimab plus axitinib showed promising antitumor activity versus toripalimab or axitinib alone in patients with treatment-naive unresectable or metastatic mucosal melanoma. Clinical trial information: NCT03941795. Research Sponsor: None.

9513 **Poster Discussion Session**

AMBER parts 1c and 1e: A phase 1 study of cobolimab plus dostarlimab in patients (pts) with advanced/metastatic melanoma.

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Background: TIM-3 and PD-1 are markers of T-cell suppression that are upregulated in melanoma. AMBER (NCT02817633) is evaluating cobolimab (TSR-022/GSK4069889), an anti-TIM-3 therapy, monotherapy or with PD-1 inhibitors, including dostarlimab, in pts with solid tumors. **Methods:** This multicenter, open-label study was conducted in 2 parts: dose escalation (Parts 1 A–D and F–H) and cohort expansion (Parts 2 A–D). Part 1C and exploratory cohort 1E (reported here) included pts with advanced/metastatic melanoma; prior therapies, except for immunotherapies, were permitted. Pts received cobolimab (100 [1C only], 300, or 900 mg IV) with dostarlimab (500 mg IV) Q3W. Part 1C primary endpoints were safety, tolerability, and recommended Phase 2 dose. Objective response rate (ORR; complete [CR] or partial [PR] response per RECIST v1.1) was a secondary endpoint in 1C and the primary endpoint in 1E (ad hoc efficacy analysis reported). An integrated safety analysis for all pts (Parts 1 and 2) receiving cobolimab with dostarlimab, regardless of tumor type or cobolimab dose, is reported here. **Results:** 28 pts were enrolled in 1C (n=10) and 1E (n=18). Most pts (n=23; 82.1%) had cutaneous disease of the skin. One pt had anorectal mucosal disease and 3 pts in the 900-mg cohort had uveal melanoma. Most pts (67.9%) had an ECOG PS=0. At data cut-off (May 19, 2021), treatment was ongoing in 5 pts. In the integrated safety analysis of pts who received cobolimab 100 mg (n=41), 300 mg (n=167), or 900 mg (n=69) with dostarlimab, treatment-related treatment-emergent AEs (TR-TEAEs) occurred in 53.7%, 57.5%, and 59.4%, respectively. The most common TR-TEAEs (any grade, ≥10% in 100 mg, 300 mg, or 900 mg groups, respectively) were fatigue (22.0%, 13.2%, 24.6%), rash (9.8%, 5.4%, 11.6%), diarrhea (4.9%, 6.0%, 10.1%), and dyspnea (2.4%, 0%, 10.1%). Grade ≥3 TR-TEAEs occurred in 12.2% (100 mg), 10.8% (300 mg), and 20.3% (900 mg); serious TR-TEAEs occurred in 7.3%, 7.8%, and 11.6%, respectively. No pts died due to TR-TEAEs; 2.4% (100 mg), 4.2% (300 mg), and 7.2% (900 mg) discontinued due to TR-TEAEs. ORR and disease control rate (DCR: stable disease [SD] ≥16 weeks, PR, or CR) are shown in the Table. Twelve pts achieved a PR and an immune-related (ir)PR (1 in 100 mg; 8 in 300 mg; 3 in 900 mg groups). Three pts achieved SD (2 in 300 mg; 1 in 900 mg groups); 8 pts had irSD (1 in 100 mg; 4 in 300 mg; 3 in 900 mg groups). **Conclusions:** Cobolimab with dostarlimab showed preliminary clinical responses in pts with advanced/metastatic melanoma and an acceptable safety profile across advanced cancers. Funding: GSK (213348). Clinical trial information: NCT02817633. Research Sponsor: GlaxoSmithKline.

Efficacy by cobolimab dose with dostarlimab.

n (%)	100 mg N=3	300 mg N=14	900 mg N=11	Total N=28
ORR	1 (33.3)*†	8 (57.1)	3 (27.3)	12 (42.9)
irORR	1 (33.3)*	8 (57.1)	3 (27.3)	12 (42.9)
DCR	1 (33.3)*†	10 (71.4)	4 (36.4)	15 (53.6)
irDCR	1 (33.3)*	11 (78.6)	4 (36.4)	16 (57.1)

*n=1 had no post-baseline tumor assessments; †n=1 was not evaluable.

9514 **Poster Discussion Session**

Phase II study of nivolumab (nivo) with relatlimab (rela) in patients (pts) with first-line advanced melanoma: Early on-treatment major pathologic response on biopsy.

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Background: A phase II study of nivo and rela was designed to evaluate the antitumor activity and mechanism of this combination and components for first-line treatment of pts with advanced melanoma. Pts received lead-in treatment with 1 cycle of nivo (480mg IV q4wk), rela (160mg IV q4wk), or nivo-rela followed by combination therapy. We assessed the effect of each lead-in treatment on immune-related pathological response (irPR) at 4-wk biopsy to develop early biomarkers of antitumor response. **Methods:** Core biopsy of an index lesion was performed at baseline and after 4 wk on-treatment. Immune characteristics of pathological response were assessed on H&E sections, including presence of tumor-infiltrating lymphocytes (TIL), neovascularization, proliferative fibrosis, plasma cells, and lymphoid aggregates. irPR score was calculated as described by Stein JE et al Ann Oncol 2019, from 0 (no irPR features) to 3 (major pathologic response on biopsy [MPRbx], ≤10% residual viable tumor). We assessed the association between irPR and radiological response (RECIST v1.1) at 4-wk evaluations. **Results:** The current cohort includes 22 pts, median age = 67, male = 13. Pts were randomized to nivo = 7, rela = 7, and nivo-rela = 8 lead-in groups. Two pts had no irPR evaluation due to early progression and unscorable tumor. Among 20 evaluable pts, proliferative fibrosis, neovascularization, plasma cells, brisk TIL, and lymphoid aggregates were identified in 50%, 35%, 26.3%, 25%, and 5% of cases, respectively. Lead-in nivo (n = 2/6), rela (n = 0/6), and nivo-rela (n = 3/8) resulted in irPR = 3 in 25% of pts. Radiological response was identified as partial response (PR) = 1/22 (4.5%), stable disease (SD) = 12/22 (54.5%), and progressive disease (PD) = 9/22 (41%). Among pts with PD, 44% received rela-, 33% nivo-, and 22% nivo-rela- lead-in. Pts with irPR score = 3 had radiological PR = 1, SD = 3, and PD = 1 at 4wks. No association was found between MPRbx and radiological response at 4 wks. **Conclusions:** Four-wk MPRbx may serve as an early biomarker of treatment response in advanced melanoma. Lead-in treatment resulted in MPRbx of 25% and was greatest with nivo-rela lead-in. Correlations between 4 wk MPRbx and later radiological responses, survival and other endpoints will be made at completion of trial accrual. Clinical trial information: NCT03743766. Research Sponsor: Bristol Myers Squibb, Melanoma and Skin Cancer SPORE Program.

	All (N = 20)	Nivo (N = 6)	Rela (N = 6)	Nivo-Rela (N = 8)
irPR = 0	20%	33.3%	33.3%	0%
irPR = 1	50%	33.3%	50%	62.5%
irPR = 2	5%	0%	16.7%	0%
irPR = 3	25%	33.3%	0%	37.5%

9515 **Oral Abstract Session**

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

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Background: Despite recent advances in the treatment of melanoma, there remains an urgent need to improve outcomes in pts with CNS mets. To date, studies evaluating intracranial activity of immunotherapies and targeted therapies have included limited numbers of pts with symptomatic CNS mets. Cohort 2 of the phase 2 Tricotel study evaluated the safety and efficacy of A + C + V in *BRAF*^{V600}-mutated melanoma with CNS mets, including symptomatic pts receiving corticosteroids. **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. Primary outcome was intracranial objective response rate (ORR; confirmed by assessments ≥4 wk apart per independent review committee [IRC]). Secondary end points were investigator-assessed intracranial ORR, extracranial ORR, overall ORR, duration of response (DOR), disease control rate, progression-free survival (PFS), overall survival (OS), and safety. Prespecified subgroup analyses were performed in pts receiving corticosteroids (>2 mg/d dexamethasone) and/or with CNS-related symptoms at baseline vs asymptomatic pts. **Results:** This study enrolled 65 pts (median age, 55 y; 63% male). At baseline, 37% were on corticosteroids and/or were symptomatic; 49% had elevated lactate dehydrogenase. Median follow-up was 9.7 mo for all pts, 10.0 mo for pts on corticosteroids and/or symptomatic at baseline (n = 24), and 9.7 mo for asymptomatic pts (n = 41). Intracranial ORR was 42% by IRC and 51% by investigator (BOR concordance: 68%). Intracranial DOR and PFS are listed in the Table. In pts on corticosteroids and/or symptomatic at baseline, ORR was 58%, DOR was 10.2 mo, and PFS was 7.2 mo by investigator; in asymptomatic pts, ORR was 46%, DOR was 5.7 mo, and PFS was 5.5 mo. Additional secondary efficacy end points will be presented. In 60 pts who received A + C + V, grade 3/4 adverse events (AEs) occurred in 70% of pts; most commonly lipase increased (27%) and blood CPK increased (17%). Serious AEs occurred in 30% of pts. AEs led to discontinuation of any study treatment in 27% of pts. **Conclusions:** Addition of A to C + V provides promising intracranial activity in pts with *BRAF*^{V600}-mutated melanoma with CNS mets, particularly in those receiving corticosteroids and/or in symptomatic pts. The safety profile of A + C + V is consistent with that observed in the IMspire150 study. Clinical trial information: NCT03625141. Research Sponsor: Roche.

Intracranial outcomes (N = 65).

	IRC	Investigator
ORR, % (95% CI)	42 (29–54)	51 (38–63)
Median DOR, mo (95% CI)	7.4 (5.7–11.0)	7.4 (5.6–10.2)
Median PFS, mo (95% CI)	5.3 (3.8–7.2)	5.8 (5.4–7.4)
6-mo PFS rate, % (95% CI)	41 (28–53)	48 (36–61)

Pembrolizumab (pembro) plus dabrafenib (dab) and trametinib (tram) in *BRAF*$^{V600E/K}$-mutant melanoma: Long-term follow-up of KEYNOTE-022 parts 1, 2, and 3.

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Background: KEYNOTE-022 (NCT02130466) was a phase 1/2 study of pembro + dab + tram or pembro + tram in patients (pts) with unresectable stage III/IV melanoma (parts 1-3) or solid tumors (parts 4 and 5). In previous analyses of pts with *BRAF*$^{V600E/K}$-mutant melanoma, pembro + dab + tram was shown to have manageable safety in parts 1-3, albeit with a higher incidence of TRAEs in part 3, and substantially improved PFS, DOR, and OS vs placebo + dab + tram in part 3, although the primary end point of a statistically significant improvement in PFS was not met. Long-term follow-up of pts with *BRAF*$^{V600E/K}$-mutant melanoma in parts 1-3 are presented. **Methods:** Eligible pts were ≥18 y with unresectable stage III/IV *BRAF*$^{V600E/K}$-mutant melanoma, ≥1 measurable lesion per RECIST v1.1, ECOG PS 0/1, and no prior systemic therapy for advanced disease. In parts 1 and 2, which involved dose finding and confirmation, pts received pembro 2 mg/kg IV Q3W + dab 150 mg PO BID + tram 2 mg PO QD (MTD). In part 3, pts were randomized 1:1 to pembro + dab + tram at MTD or placebo + dab + tram. Primary end points were safety, tolerability, and MTD (parts 1 and 2); ORR per RECIST v1.1 by investigator review (part 2); and PFS per RECIST v1.1 by investigator review (part 3). Data cutoff was July 14, 2021. **Results:** Median (range) study follow-up was 72.9 mo (68.4-84.5) in parts 1 and 2 (n = 15) and 61.2 mo (50.7-67.5) for all pts (n = 120; 60 each arm) in part 3. Safety of pembro + dab + tram in parts 1 and 2 was consistent with prior reports; grade 3/4 TRAEs occurred in 11 pts (73%), and no additional DLTs occurred. ORR in parts 1 and 2 was 67% (95% CI, 38-88), which was similar to that reported at an earlier data cut (73% [95% CI, 45-92]); median DOR was 19.4 mo (95% CI, 2.8-NR), median OS was NR (95% CI, 10.3-NR), 48-mo OS rate was 60%, median PFS was 15.2 mo (95% CI, 4.2-NR), and 48-mo PFS rate was 28% (Ribas A et al. *Nat Med*. 2019;25:936-940). In part 3, median PFS was 17.0 mo (95% CI, 11.3-NR) for pembro + dab + tram vs 9.9 mo (95% CI, 6.7-15.6) for placebo + dab + tram (HR, 0.46; 95% CI, 0.29-0.74) and 24-mo PFS rate was 47% vs 16%, and median OS was 46.3 mo (95% CI, 23.9-NR) vs 26.3 mo (95% CI, 18.2-38.6); and 24-mo OS rate was 63% vs 52%, respectively. ORR was 65% (95% CI, 52-77) for pembro + dab + tram vs 72% (95% CI, 59-83) for placebo + dab + tram; median DOR was 30.2 mo (95% CI, 14.1-NR) vs 12.1 mo (95% CI, 6.0-15.7). Safety in part 3 was similar to prior reports; grade 3-5 TRAEs occurred in 42 pts (70%) in the pembro + dab + tram arm vs 27 pts (45%) in the placebo + dab + tram arm (Ferrucci PF et al. *J Immunother Cancer.* 2020;8:e001806). No additional grade 5 TRAEs occurred (1 grade 5 pneumonitis had occurred at prior analysis). **Conclusions:** At long-term follow-up, first-line pembro + dab + tram continued to show improved PFS, DOR, and OS compared with placebo + dab + tram in pts with *BRAF*$^{V600E/K}$-mutant melanoma. TRAEs were more common with pembro + dab + tram but no new safety signals were identified. Clinical trial information: NCT02130466. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

9517 **Poster Discussion Session**

Newly updated activity results of alrizomadlin (APG-115), a novel MDM2/p53 inhibitor, plus pembrolizumab: Phase 2 study in adults and children with various solid tumors.

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Background: Alrizomadlin restores *TP53* function, activating p53-mediated apoptosis in tumor cells with wild-type *TP53* and/or *MDM2* amplification. Alrizomadlin also functions as a host immunomodulator and may restore antitumor activity in pts with cancers that progressed on PD-1/PD-L1 inhibitors. **Methods:** This US/Australian multicenter trial evaluated alrizomadlin, an investigational MDM2-selective, small-molecule inhibitor, combined with pembrolizumab, in pts with unresectable/metastatic melanoma that progressed on I-O drugs; pts with malignant peripheral nerve sheath tumor (MPNST), well-differentiated/dedifferentiated liposarcoma, non-small cell lung cancer (NSCLC), or solid tumors with *ATM* mutations that progressed on available standard therapy; or pts for whom therapy was unavailable. Eligible pts had ECOG performance status of 0-2 and, if present, stable brain metastases. Alrizomadlin 150 mg PO was administered QOD for 2 consecutive weeks, with 1 week off, and pembrolizumab 200 mg IV over 30 minutes on Day 1 of a 21-day cycle. **Results:** As of November 3, 2021, preliminary and interim results are reported for 130 pts in 6 cohorts: melanoma (n = 44), NSCLC (n = 26), *ATM* mutation (n = 18), liposarcoma (n = 17), urothelial (n = 13), and MPNST (n = 12). In the melanoma cohort, confirmed ORR by RECIST, (PR + CR) was 13% (2 CRs + 3 PRs/38 efficacy evaluable [EE] pts). In cutaneous and uveal melanoma subcohorts, confirmed ORR was 24% (2 CRs + 2 PRs/17 EE pts) and 9% (1 PR/11 EE pts), respectively. In the MPNST cohort, the clinical benefit rate, defined by confirmed ORR + SD of > 4 cycles, was 40% (4 SDs/10 EE pts). Additional confirmed PRs were reported in NSCLC, urothelial, and liposarcoma cohorts (1 each). Common treatment (alrizomadlin or pembrolizumab)-related adverse events (TRAEs; ≥ 10%) were nausea (62%), thrombocytopenia (39%), vomiting (38%), fatigue (38%), decreased appetite (29%), diarrhea (25%), neutropenia (15%), and anemia (12%). Grade 3^{+} TRAEs (≥ 5%) included thrombocytopenia (23%), neutropenia (10%), and anemia (7%). A total of 16 pts discontinued treatment due to AEs; 6 were treatment related, including grade 4 thrombocytopenia (n = 3), grade 2 vomiting (n = 1), grade 2 fatigue (n = 1), and grade 2 posterior reversible encephalopathy syndrome (PRES; n = 1). A total of 10 pts reported treatment-related SAEs: 1 each of abdominal pain, asthenia, colitis, febrile neutropenia, hypophysitis, peripheral edema, overdose, PRES, pulmonary embolism, pyrexia, and thrombocytopenia. **Conclusions:** Alrizomadlin, combined with pembrolizumab, is well tolerated and demonstrates preliminary antitumor activity in multiple tumor types and may restore antitumor effects in pts with cancer resistant or intolerant to I-O drugs. Internal study identifiers: APG-115-US-002; Keynote MK-3475-B66. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Corp. Ltd (Hong Kong).

9518 **Poster Discussion Session**

Primary analysis of a phase 2, open-label, multicenter trial of talimogene laherparepvec (T-VEC) plus pembrolizumab (pembro) for the treatment (Tx) of patients (pts) with advanced melanoma (MEL) who progressed on prior anti–PD-1 therapy: MASTERKEY-115.

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Background: Despite advances in anti–PD-1–based Tx for MEL, an unmet need remains for immunotherapy failure in advanced metastatic or unresectable MEL. Also, there is a growing population of pts who received adjuvant anti–PD-1 and recurred; yet trials to address this population are lacking. Combination Tx with T-VEC, an oncolytic viral intratumoral Tx designed to produce GM-CSF, and pembro, an anti–PD-1 agent, may overcome immunotherapy failure. We report the MASTERKEY-115 primary analysis on the efficacy and safety of T-VEC + pembro in pts with advanced MEL who had progressive disease (PD) on prior anti–PD-1. **Methods:** This open-label, single-arm, multicenter, phase 2 study (NCT04068181) enrolled pts at 26 international sites (Jan 2020–Feb 2021). Cohorts 1 and 2, primary and acquired resistance, respectively, received anti–PD-1 in a locally recurrent or metastatic setting and had PD within 12 wks of the last anti–PD-1 dose. Cohorts 3 and 4 included only pts who received adjuvant anti–PD-1 and were disease-free for < 6 mos (Cohort 3) or ≥ 6 mos (Cohort 4) before confirmed PD. Eligible pts had histologically confirmed unresectable or metastatic stage IIIB–IVM1d MEL, measurable and injectable disease, ECOG PS 0/1, and progressed on anti–PD-1 directly before enrollment. T-VEC at standard dosage and pembro 200 mg were given Q3W. The primary endpoint was objective response rate (ORR). Key secondary endpoints were complete response (CR) rate, progression-free survival (PFS), and safety. Tx decisions were per modified immune-related response criteria (irRECIST). **Results:** 72 pts (median age, 65 y) were enrolled. Of the 71 evaluable pts, 37 (52.1%) had stage IVM1b–d disease, 30 (42.3%) had confirmed PD-L1–positive tumor (CPS ≥ 1%), 20 (28.2%) had a *BRAF*^{V600} mutation, and 21 (29.6%) had LDH > 1ULN. At data cutoff (Aug 2021), 47 (65.3%) pts remained on study. ORR was 0%, 6.7%, 40%, and 46.7% in cohorts 1–4, respectively (table). Any-grade Tx-related adverse events (TRAEs) were reported in 54 (76.1%) pts; the most common were pyrexia (29.6%), fatigue, and influenza-like illness (15.5% each). Grade ≥ 3 TRAEs occurred in 9 (12.7%) pts. **Conclusions:** T-VEC + pembro showed manageable safety in pts with advanced MEL after anti–PD-1 failure; the promising ORR observed in pts who progressed on prior adjuvant anti–PD-1 warrants further analysis. Clinical trial information: NCT04068181. Research Sponsor: Amgen Inc; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	Cohort 1 (N = 26)	Cohort 2 (N = 15)	Cohort 3 (N = 15)	Cohort 4 (N = 15)
ORR[a], n (%)	0	1 (6.7)	6 (40.0)	7 (46.7)
95% CI		0.2–32.0	16.3–67.7	21.3–73.4
PFS[b], Median (mos), 95% CI	5.5	8.2	NE	NE
	2.8–NE	2.7–15.0		
CR[b], n (%)	0	0	2 (13.3)	2 (13.3)
PR[b], n (%)	1 (3.8)	1 (6.7)	6 (40.0)	5 (33.3)
SD[b], n (%)	12 (46.2)	5 (33.3)	3 (20.0)	6 (40.0)
PD[b], n (%)	5 (19.2)	4 (26.7)	1 (6.7)	0

[a]Per modified RECIST1.1; [b]Per modified irRECIST; NE, not estimable; PR, partial response; SD, stable disease

9519 **Poster Discussion Session**

Long-term outcomes of a phase II trial of neoadjuvant immunotherapy for advanced, resectable cutaneous squamous cell carcinoma of the head and neck (CSCC-HN).

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Background: In a pilot phase II trial, we investigated the use of neoadjuvant immunotherapy to induce a pathologic response in patients with stage III/IV (M0) cutaneous squamous cell carcinoma of the head and neck (CSCC-HN). Here, we report the long-term outcomes according to pathologic response. **Methods:** Patients with newly diagnosed or recurrent stage III/IV (M0) (AJCC 8th Ed) CSCC-HN were treated with 2 doses of cemiplimab 350 mg intravenously every 3 weeks prior to surgery. The primary endpoint was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included safety, pathologic response, disease-free and overall survival. **Results:** Of 20 patients enrolled, 7 (35%) had recurrent disease and 12 (60%) were stage IV on presentation. Neoadjuvant immunotherapy was generally well-tolerated and there were no surgical delays. Adverse events (AEs) were observed in 7 (35%) patients; 1 (5%) grade 3 diarrhea, 6 (30%) ≤ grade 2 AEs. ORR by RECIST was 30%. However, 85% (17/20) achieved a pathologic response (≤50% viable tumor), with pathologic complete response (pCR) in 11 (55%), major pathologic response (MPR, ≤10% viable tumor) in 4 (20%) and pathologic partial response (pPR, >10% and ≤50% viable tumor) in 2 (10%). Patients with a pCR did not receive planned radiotherapy after surgery. Patients who did not have a pathologic response (> 50% viable tumor) either progressed and died (1, 5%) or developed recurrence (2, 10%) despite surgery and adjuvant radiation or chemoradiation. At a median follow up of 34.5 months (range: 7.7-42.7), none of the patients who achieved a pathologic response have recurred. **Conclusions:** Consistent with other cancer types, pathologic response to neoadjuvant immunotherapy is durable in patients with advanced, resectable CSCC-HN. Adjuvant radiation therapy may be spared in patients who achieve a pCR and warrants further investigation. Clinical trial information: NCT03565783. Research Sponsor: Regeneron.

9520 **Poster Discussion Session**

Immunotherapy followed by cetuximab in locally advanced/metastatic (LA/M) cutaneous squamous cell carcinomas (cSCC): The I-TACKLE trial.

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Background: In LA/M cSCC patients (pts), immunotherapy with pembrolizumab (P) and cemiplimab showed an overall response rate (ORR) of 34-49%, with durable antitumor activity. However, primary and acquired resistance represents a therapeutic challenge. In cSCC, monotherapy with cetuximab (C) showed promising signs of activity (ORR 28%), but with limited duration of response. This study aims at reverting P resistance by adding C, leveraging on its mechanism of action in reducing immune escape process. **Methods:** I-TACKLE is an open-label, nonrandomized, phase II trial in pts with LA/M cSCC conducted in 3 Italian centers. Eligible pts had LA/M cSCC not manageable with surgery or radiation and with ECOG PS= 0 or 1. They received intravenous P 200 mg every 3 weeks. In case of partial (PR) or complete response (CR), pts continued to receive P alone. In case of stable disease (SD) or progression (PD), pts received C (400 mg/sm loading dose, then weekly 250 mg/sm) in addition to P until progression. The primary endpoint was cumulative ORR by single agent or by combination strategy; safety, PFS (since start of P and P+C), OS and duration of response (DOR) were secondary endpoints. **Results:** Between May 2019 and April 2021, 43 pts were enrolled and treated with P. Table 1 depicts population baseline features. The median follow up was 24 (range 7-30) months. Twenty-three pts underwent the combination treatment (17/23 due to PD and 6/23 due to SD); 21 of them due to primary resistance and 2 because of acquired resistance. Median treatment exposure was 3 and 4 months to P and combination therapy, respectively. Cumulative ORR was 63% [95% confidence interval 48-77], including 19/43 (44%) pts with response to P and 8/21 (38%) with response to combination strategy after primary resistance to P. Both pts experiencing an acquired resistance to P obtained PR when C was introduced. Overall, 10/23 pts (44%) obtained a response to combination therapy. Median DOR and OS were not reached both with P alone and with P+ C. One-year PFS was 51% with P alone and 42% with P+C. Overall, grade 3-4 treatment-related adverse events occurred in 7/43 (16%) pts during treatment with P and 8/23 (35%) pts during P+C, mostly dermatitis 7/23 (30%). Three out of 43 (7%) pts discontinued treatment because of toxicity, one pancreatitis, one impaired renal function and one for worsening of clinical condition, all during treatment with P. Four patients died during treatment, due to PD. **Conclusions:** In LA/M cSCC, the addition of C to P reverts primary and acquired resistance, with manageable toxicities. The sequential approach deserves to be studied in future clinical trials. Clinical trial information: NCT03666325. Research Sponsor: Merck Sharp & Dohme MISP (Merck Investigator Studies Program).

Baseline characteristics of pts.

Characteristics	N◦ (%)
Median Age (range), years	79 (48-96)
Male	34 (79)
ECOG PS 0	11 (26)
Previous treatments	
Chemotherapy	7 (16)
Radiation therapy	21 (49)
T3-T4	35 (81)
N2-N3	17 (40)
M1	13 (30)
Head and Neck primary T	30 (70)

9521 **Poster Session**

A retrospective study of ipilimumab plus nivolumab in anti–PD-L1/PD-1-refractory merkel cell carcinoma.

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Background: Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine carcinoma with a high recurrence and mortality rate. Immune checkpoint inhibitors (ICIs) targeting the PD-L1/PD-1 axis have shown significant clinical benefit with durable responses in patients with advanced MCC leading to regulatory approvals by the U.S. Food and Drug Administration for two agents: avelumab (anti-PD-L1) and pembrolizumab (anti-PD-1). However, many patients (~50%) with advanced MCC treated with ICI do not experience tumor regression. Studies regarding systemic therapy options following progression due to primary or acquired resistance to immunotherapy are limited and management remains a clinical challenge. In this retrospective study, we evaluated objective clinical response to combination ipilimumab and nivolumab (ipi-nivo) salvage therapy in advanced MCC refractory to anti-PD-L1/PD-1 treatment. **Methods:** We reviewed the electronic medical record at Mass General Brigham associated institutions to identify patients with advanced MCC that progressed on upfront immunotherapy (e.g., pembrolizumab, avelumab or nivolumab) and were re-challenged with combination ipi-nivo between 2016 to 2021. Patients treated with prior surgery, radiation, or cytotoxic chemotherapy after progressing on immunotherapy were not excluded. Responses to ipi-nivo were evaluated for every patient at each re-staging/interval assessment following baseline analysis utilizing Response Evaluation Criteria in Solid Tumors (RECISTv1.1) as well as immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) to ensure conventional RECIST did not underestimate the benefit of ipi-nivo. **Results:** Four patients (31%) experienced grade III/IV immune-related adverse events. No patients (0/13) in this case series achieved an objective response via RECISTv1.1/irRECIST. Stable disease was seen in 23% (3/13) and the median progression-free survival was 1.3 months (90% CI, 1.1-1.5). The median overall survival from the initiation of ipi-nivo was 4.7 months (95% CI, 3-17). **Conclusions:** This study suggests limited, if any, clinical benefit of ipi-nivo in patients with advanced anti-PD-L1/anti-PD-1-refractory MCC. New strategies for second-line treatment of MCC are needed and referral to innovative clinical trials should be a priority for patients with refractory metastatic MCC. Research Sponsor: Project Data Sphere; ECOG-ACRIN, Fund for Medical Discovery Clinical Research Fellowship Award (MGH-ECOR), American Skin Association.

9522 **Poster Session**

Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067.

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Background: Durable clinical benefit has been achieved with nivolumab (NIVO) + ipilimumab (IPI), including an overall survival (OS) of 49% and a melanoma-specific survival (MSS) of 56%, with median MSS not reached (NR) at 6.5-y minimum follow-up. Here we report sustained efficacy outcomes at 7.5 y. **Methods:** Patients (pts) with previously untreated, unresectable stage III/IV melanoma were randomly assigned 1:1:1 and stratified by PD-L1 status, *BRAF* mutation status, and metastasis stage to receive NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W, followed by NIVO 3 mg/kg Q2W (n = 314); NIVO 3 mg/kg Q2W + placebo (n = 316); or IPI 3 mg/kg Q3W for 4 doses + placebo (n = 315) until progression or unacceptable toxicity. Co-primary endpoints were progression-free survival (PFS) and OS with NIVO + IPI or NIVO alone versus IPI. **Results:** With a minimum follow-up of 7.5 y, median OS remained stable at 72.1 mo (NIVO + IPI), 36.9 mo (NIVO), and 19.9 mo (IPI); median MSS was NR, 49.4 mo, and 21.9 mo, respectively (Table). While the objective response rate remained stable at 58% (NIVO + IPI), 45% (NIVO), and 19% (IPI), median duration of response had now been reached for NIVO at 90.8 mo and remains NR and 19.2 mo for NIVO + IPI and IPI, respectively. Subsequent systemic therapy was received by 36%, 49%, and 66% of NIVO + IPI-, NIVO-, and IPI-treated patients, respectively, and median time to that therapy was NR (95% CI, 45.9–NR), 24.7 mo (16.0–38.7), and 8.0 mo (6.5–8.7). Of patients alive at 7.5 y, 106/138 (77%, NIVO + IPI), 80/115 (70%, NIVO), and 27/60 (45%, IPI) were off treatment and had never received subsequent systemic therapy. No change to the safety summary was observed with additional follow-up; updated health-related quality of life data will be reported. Of the 10 new deaths since the 6.5-y follow-up (ie, 5 NIVO + IPI; 3 NIVO; 2 IPI), none were treatment-related; 4 were due to melanoma progression; 1 was due to an unknown cause; and 5 were due to other causes, but not associated with a COVID diagnosis. **Conclusions:** The 7.5-y follow-up continues to demonstrate the durability of responses with NIVO + IPI and an ongoing survival plateau. A substantial difference in median OS and MSS between patients treated with NIVO + IPI or NIVO was observed in descriptive analyses. Clinical trial information: NCT04540705. Research Sponsor: Bristol Myers Squibb, Pharmaceutical/Biotech Company, Grant P30CA008748 to J. D. W. from the National Cancer Institute, and a grant to J. L. from the National Institute for Health Research Royal Marsden–Institute of Cancer Research Biomedical Research Centre.

	NIVO + IPI(n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS: all pts, mo (95% CI)	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
7.5-y OS rate: all pts, % (95% CI)	48 (42–53)	42 (36–47)	22 (18–27)
***BRAF* mutant subgroup**	57 (47–66)	42 (32–52)	25 (17–34)
Median MSS: all pts, mo (95% CI)	NR (71.9–NR)	49.4 (35.1–NR)	21.9 (18.1–27.4)
7.5-y MSS rate: all pts, % (95% CI)	55 (50–61)	47 (41–52)	26 (21–32)
Median PFS: all pts, mo (95% CI)	11.5 (8.9–20.0)	6.9 (5.1–10.2)	2.9 (2.8–3.1)
7.5-y PFS rate: all pts, % (95% CI)	33 (27–39)	27 (22–33)	7 (4–11)

9523 **Poster Session**

Androgen receptor blockade promotes response to BRAF/MEK-targeted therapy.

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Background: Treatment with BRAF+/-MEK inhibition (BRAF+/-MEKi) has revolutionized treatment in melanoma and other cancers, but resistance is common and innovative treatment strategies are needed. Sexual dimorphism in response to BRAF+/-MEKi have been noted, but mechanisms behind this are poorly understood and hormonal modulation has not been well-studied in this setting. **Methods:** We examined outcomes by sex in five clinical cohorts of patients (pts) (total n = 792, 362 female, 430 male) with *BRAF*-mutated melanoma who were treated with BRAF/MEKi in either the neoadjuvant or metastatic setting. Rates of major pathologic response (MPR), clinical benefit (CB), progression free survival (PFS) relapse-free survival (RFS) and overall survival (OS) were assessed. Translational research studies were performed on available pre- and on-treatment tumor samples (n = 27 pts) including RNA sequencing and profiling androgen receptor (AR) expression. Parallel studies were performed in preclinical models to assess the effect of sex and AR modulation on response to BRAF+/-MEKi. **Results:** In this study, improved rates of MPR, CB, PFS and OS were observed in female vs male pts. Specifically, female patients treated with neoadjuvant BRAF+MEKi showed significantly higher rates of MPR (66% v. 14%, p = 0.001), and improved RFS (64% versus 32% at 2 years, p = 0.021) vs male pts in the neoadjuvant setting (n = 51). These findings were not observed in a 2nd smaller trial of pts (n = 35), but were validated in a cohort of pts with unresectable metastatic melanoma treated with BRAF+MEKi (n = 69), with significantly higher rates of CB (80% v. 68%, p = 0.022) and PFS (12 v. 7 months, p = 0.003) in female vs male pts. Data from several published trials was analyzed (COMBI-D and METRIC trials), demonstrating improved PFS/OS at 2 years in female vs male pts treated with combined BRAF/MEKi (n = 211; p = 0.03 and, p = 0.04) and in female vs male pts treated with MEKi monotherapy (n = 206; p = 0.04 and p = 0.002), but not in female vs male pts treated with BRAFi monotherapy (n = 211; p = 0.21 and 0.095). Significantly higher expression AR expression was observed in available on- vs pre-treatment samples from male pts (p = 0.01), suggesting that treatment with BRAF/MEKi may induce AR expression in tumors. Findings were recapitulated in several preclinical models, and treatment with pharmacologic inhibitors of AR signaling (enzalutamide) in combination with BRAF/MEKi was associated with significantly enhanced anti-tumor activity in both male and female mice (p = 0.003 and p < 0.0001). Conversely, systemic treatment with testosterone was associated with significantly impaired tumor control in male and female mice (p = 0.021 and < 0.001). **Conclusions:** These data suggest that AR blockade may promote BRAF/MEKi response in melanoma, warranting further investigation in clinical trials. The impact of AR signaling, and modulation should be studied in MAPK-targeted therapy across other cancer types. Research Sponsor: U.S. National Institutes of Health.

9524 **Poster Session**

Tumor mutational burden (TMB) in immune checkpoint inhibitor (ICI)-naïve and -experienced patients with metastatic melanoma treated with lifileucel, a tumor-infiltrating lymphocyte (TIL) cell therapy.

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Background: Cutaneous melanoma is characterized by high TMB, which is associated with increased tumor-specific neoantigen expression (Schumacher Science 2015) and an increased response rate to ICI (Yarchoan NEJM 2019). The TMB in tumors that recur/progress after ICI is not well defined. Lifileucel is a one-time, autologous TIL cell therapy under investigation for treatment of patients (pts) with advanced melanoma. We conducted a matched case-control study of prospectively enrolled pts with advanced melanoma treated with lifileucel in the ICI-naïve (IOV-COM-202 trial, Cohort 1A [C1A]) and post-ICI (C-144-01 trial, Cohort 2 [C2]) setting to investigate the potential association between prior ICI therapy, TMB, and response to lifileucel. **Methods:** All pts had unresectable or metastatic melanoma. Available cases from C1A (ICI-naïve pts receiving lifileucel + pembrolizumab [pembro]) were matched to controls from C2 (pts receiving lifileucel alone after progression on antiPD-1/PD-L1 therapy); 3 controls per case were matched at least for BRAF status and disease stage at study entry, and if possible, for anatomic site of tumor harvest. Lifileucel regimen was similar in C1A and C2. In C1A, 1 dose of pembro was given after tumor harvest and before nonmyeloablative lymphodepletion and resumed after lifileucel per standard treatment, for up to 2 y. Objective response rate (ORR) was assessed by investigators per RECIST v1.1. TMB of the resected tumor was measured using the ImmunoID NeXT (C1A) or PGDx elio (C2) platform; a validated conversion factor was used to compare TMB between platforms (Vega Ann Oncol 2021). High TMB was defined as ≥10 mut/MB. **Results:** Seven pts in C1A and 21 in C2 were included in the case-control study and had ORR of 71.4% and 38.1%, respectively. The percentage of pts with high TMB was 57.1% in C1A and 19.0% in C2 (P = 0.1). ORR in the low and high TMB groups was 66.7% and 75.0%, respectively, in C1A and 41.1% and 25.0% in C2; 60% of responders in C1A and 12.5% in C2 had high TMB. In logistic regression analysis adjusted for cohort, TMB was not associated with response to lifileucel (odds ratio, 1.0; 95% CI, 0.91.1; P = 0.8). Data on tumor mutations and neoantigens, T-cell receptor repertoire, and tumor microenvironment profile will be presented. **Conclusions:** Our preliminary data indicate that the efficacy (ORR) of lifileucel may be independent of TMB, regardless of treatment setting, consistent with its proposed immune checkpoint pathway-independent mechanism of action. The percentage of patients with high TMB tended to be lower in tumors with prior ICI exposure than in those that were ICI-naïve. Clinical trial information: NCT03645928; NCT02360579. Research Sponsor: Iovance Biotherapeutics.

9525 **Poster Session**

Atezolizumab plus bevacizumab in patients with unresectable or metastatic mucosal melanoma: A multicenter, open-label, single-arm phase 2 study.

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Background: Anti-programed cell death-1 (PD-1) monotherapy is a part of the standard therapy for cutaneous melanoma but has demonstrated low efficacy in mucosal melanoma. This study evaluated the efficacy and safety of atezolizumab plus bevacizumab as a first-line therapy in patients with advanced mucosal melanoma. **Methods:** This multicenter, open-label, single-arm, phase 2 study utilized a Simon's two-stage design. Atezolizumab (fixed-dose, 1200 mg) and bevacizumab (7.5 mg/kg) were administered by intravenous infusion every 3 weeks. The primary endpoint was objective response rate (ORR), determined by the investigator per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and safety with adverse events summarized using NCI-CTCAE v5.0. **Results:** In total, 43 patients were enrolled, including 20 (46.5%) with unresectable and 23 (53.5%) with metastatic mucosal melanoma. Median follow-up was 13.4 months at data cut-off (July 30, 2021). Forty patients were evaluable for response: In stage I analysis set (n=22), the best confirmed ORR according to RECIST v1.1 was 40.9% (9/22; 95% CI 20.7-63.7), including one CR and eight PRs. The ORR in the FAS population was 45.0% (95% CI, 29.3-61.5) (1 CR, 17 PRs) and the DCR was 65.0% (95% CI, 48.3-79.4). The median PFS was 8.2 months (95% CI, 2.7-9.6), the 6- and 12-month PFS rates were 53.4% (95% CI, 36.6-67.6) and 28.1% (95% CI, 14.2-43.9), respectively. The median OS was not reached (NR) (95% CI, 14.4-NR). The 6- and 12-month OS rates were 92.5% (95% CI, 78.5-97.5) and 76.0% (95% CI, 57.1-87.5), respectively. The median DOR was 12.5 months (95% CI, 5.5-NR). Overall, 90.7% (39/43) of patients experienced treatment-related adverse events, and 25.6% (11/43) experienced grade ≥ 3 events. **Conclusions:** Atezolizumab in combination with bevacizumab showed promising efficacy and a manageable safety profile in patients with advanced mucosal melanoma. Research Sponsor: Shanghai Roche Pharmaceuticals Ltd., China. Clinical trial information: NCT04091217. Research Sponsor: Shanghai Roche Pharmaceuticals Ltd., Shanghai, China.

9526 **Poster Session**

Encorafenib plus binimetinib in patients with locally advanced, unresectable, or metastatic BRAF^{V600}-mutant melanoma: Updated data from the multicenter, multinational, prospective, non-interventional longitudinal study BERING^{MELANOMA}.

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Background: For the treatment of advanced BRAF^{V600}-mutated melanoma, targeted BRAF/MEK-inhibition is a standard of care. Encorafenib + binimetinib (EB) were approved 2018 in the EU and 2019 in Switzerland, based on positive results from COLUMBUS (NCT01909453), median progression-free survival (PFS) 14.9 mo (5-yr PFS: 23%), overall survival (OS) 33.6 mo (5-yr OS: 35%). As data from controlled trials are based on selected populations, BERING^{MELANOMA} investigates EB-use under real-world conditions in a broader population. **Methods:** BERING^{MELANOMA} (NCT04045691) is an ongoing, multi-national, prospective, longitudinal, non-interventional study. It analyzes the effectiveness (prim. endpoint: 1-yr PFS-rate), QoL and safety of EB-therapy in the unresectable advanced or metastatic setting under real-world conditions, focusing on the first- (1L) and second-line setting including an evaluation of the impact of prognostic factors. The project aims to enroll up to 750 patients (pts) in a total of 80 German, Austrian and Swiss sites (study duration: 8 yrs). So far (10/2019-01/2022), 280 pts have been included. Pts with prior BRAF-/MEK-inhibition (except adjuvant use completed > 6 mo) and > 1 prior therapy line with CPI in the palliative setting were excluded (adjuvant CPI allowed). **Results:** Here we present the 2nd planned interim snapshot based on the initial 200 enrolled pts (186 treated / 182 evaluable; median FU: 14.2 mo). This analysis set shows a median age of 60.5 yrs (range 20.0-89.0), 45% of pts were female. 87% presented with distant metastases (brain: 30%), with an involvement of ≥3 organ systems in 51% and elevated LDH in 43%. 54% of pts underwent any prior systemic therapy (adjuvant: 30%; 1L CPI palliative: 24%, mainly with ipilimumab + nivolumab). EB was mainly administered in the 1L-setting (60%). Main reasons for EB-selection were: efficacy (44%), physician's preference (34%), QoL (17%). Median estimated EB treatment duration was 11.6 mo (95%CI 8.8-18.6), median relative dose intensity for both drugs: 100%, main reasons EB-discontinuation: PD (55%), toxicity (16%). Treatment adaptations were required in 40% of pts (interruption E 26%, B 29%), toxicity as main reason (E 26%, B 29%). Adverse events were reported in 86% of pts (grade 3/4: 34%), mainly (≥10%, all grades): diarrhea, nausea, fatigue (each 17%), CK increase (16%), GGT increase (11%). No fatal toxicities were observed. **Conclusions:** This 2nd interim snapshot shows an investigation of EB in a real-world population with advanced disease. Despite the poorer prognosis configuration as compared to the pivotal study, the observed tolerability profile is largely consistent with data derived from COLUMBUS without any new safety signals. The 3rd interim snapshot will be performed after enrollment of 300 pts. Research Sponsor: Pierre Fabre Pharma.

9527 **Poster Session**

Dabrafenib (D) and trametinib (T) plus spartalizumab (S) in patients (pts) with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma: Three-year overall survival (OS) data from the randomized part 3 of the phase III COMBI-i trial.

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Background: Combination of immune checkpoint inhibitors and targeted therapy may produce durable and deep response in a higher proportion of pts with *BRAF* V600–mutant unresectable or metastatic melanoma. A recent report from the randomized, double-blind, placebo (PBO)-controlled Part 3 of the Phase 3 COMBI-i trial (NCT02967692) failed to show a statistically significant progression-free survival (PFS) benefit (hazard ratio (HR) of 0.82 (95% CI, 0.66–1.03, *p*=.042)). Here, we report 3-year OS data from COMBI-i part 3. **Methods:** Eligible pts were randomized 1:1 to receive either S+D+T (n = 267; S 400 mg IV Q4W + D 150 mg orally BID + T 2 mg orally QD) or PBO+D+T (n = 265), until progression or unacceptable toxicity. Although the primary endpoint of PFS was not met, exploratory OS and safety analyses were performed. OS was summarized descriptively using Kaplan–Meier methods and HR was estimated using a stratified cox regression model. **Results:** As of October 19, 2021 (median follow-up, 42.8 months), the median OS was not reached in S+D+T arm and was 40.4 months with PBO+D+T (HR 0.796; 95% CI, 0.615–1.029). There were 113 (42.3%) deaths in the S+D+T and 126 (47.5%) in the PBO+D+T. Estimated 2-year and 3-year OS rates were 67.7% (95% CI 61.6–73.1) and 60.1% (95% CI 53.8–65.8) with S+D+T vs 61.9% (95% CI 55.6–67.5) and 52.9% (95% CI 46.6–58.9) with PBO+D+T, respectively. An OS benefit was observed with S+D+T in these prespecified subgroups – Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 (HR 0.50; 95% CI, 0.32–0.8), age ≥65 years (HR 0.58; 95% CI, 0.36–0.94), PD-L1 negative (< 1%) (HR 0.62; 95% CI, 0.42–0.91), sum of lesion diameters ≥ 66 mm at baseline (HR 0.63; 95% CI, 0.43–0.91) and metastatic sites ≥ 3 (HR 0.66; 95% CI, 0.47–0.94). Adverse events (AEs) irrespective of study treatment relationship were observed in 99.3% of pts in S+D+T vs 97.3% in PBO+D+T. The most common AEs (in > 30%; all grades) were pyrexia, diarrhea, and nausea. Grade ≥3 treatment-related AEs (TRAEs) occurred in 56.9% vs 35.2% of pts treated with S+D+T vs PBO+D+T, respectively. Dose reductions of D and T due to AEs were more frequent in the S+D+T arm than PBO+D+T arm (47.2% vs 25.4% and 45.7% vs 25.4%, respectively), contributing to a lower relative dose intensity; the TRAEs leading to discontinuation of all 3 study drugs occurred in 13.5% vs 8% of pts, respectively. **Conclusions:** Results from this landmark 3-year OS analysis from COMBI-i- part 3 was consistent with the primary analysis, while the PBO+D+T showed a higher OS rate than previously observed for D+T alone in COMBI D/V studies, with a longer median follow-up. Subgroup analyses showed that ECOG PS 1, age ≥65 years, negative PD-L1 status and high tumor burden were associated with better OS in S+D+T in terms of HR. Clinical trial information: NCT02967692. Research Sponsor: Novartis.

9528 **Poster Session**

Efficacy and safety of nivolumab for locally advanced or metastatic cutaneous cell carcinoma (NIVOSQUACS trial).

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Background: Cutaneous squamous cell carcinoma (cSCC) is the second most frequent skin cancer and considered as a tumor with strong immunogenicity. Consistently, immune checkpoint-inhibition with programmed death (PD)-1 antibodies has become the novel standard of care in the treatment of advanced cSCC. In this study, we evaluated efficacy and safety of the PD-1 antibody nivolumab in patients with locally advanced or metastatic cSCC, including individuals with concomitant hematological malignancies (CHM) – a highly vulnerable subgroup of cSCC patients typically excluded from clinical trials. **Methods:** This phase II, open-label, single-arm multicentre study included patients aged ≥ 18 years with histologically confirmed locally advanced and/or metastatic cSCC and at least one measurable lesion according to RECIST v1.1. Enrolled patients received nivolumab 240 mg intravenously over 30 min every 2 weeks for up to 2 years. A sample size of 31 patients was needed to provide 90% power to detect an objective response rate (ORR) of at least 12.6% after 24 weeks with a type I error of 5% assuming a dropout-rate of 15%. The primary endpoint was investigator assessed ORR as per RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). **Results:** Between July 2017 and October 2020, 31 patients with advanced cSCC, including 11 patients with CHM, were enrolled and received at least one dose of nivolumab. The median age was 80 years (range 66-92) and the majority of patients was male (71%). Upon enrollment, 19.4% of patients had locally advanced, 51.6% loco-regional metastatic and 25.8% distant metastasic disease. Seven patients (22.6%) had received one prior systemic therapy for cSCC. At data-cut-off (March 2021; week-24 RECIST assessment completed in all available patients), five patients (16.1%) were still on treatment, one patient completed treatment per protocol, whereas 25 patients had discontinued therapy. Of 29 patients who were evaluable for response assessment, 12 patients achieved a partial and 7 a complete response, resulting in a best ORR of 65.2% (95% CI: 45.7% - 82.1%), a DCR of 68.9% (95% CI: 50.8%-82.7%) and a median PFS of 11.1 months (95% CI: 3.7 - 12.9). Treatment related adverse events occurred in 18 patients (58.1%) and led to nivolumab discontinuation in two patients (6.5%). Subgroup analysis of patients with CHM revealed a best ORR of 55.6% (95% CI: 21.2% - 86.3%), a DCR of 66.7% (95% CI: 35.4% -87.9%) and a median PFS of 10.9 months (95% CI: 0.6 - 21.4). Median OS in this subgroup was 20.7 months (95% CI: 6.5 - 35.0), whereas overall median OS was not reached. **Conclusions:** Nivolumab showed a robust antitumor-activity similar to other anti-PD-1 agents in advanced cSCC. Although ORR and OS were slightly reduced in patients with CHM, nivolumab proved effectiveness also in this subgroup while no new safety signals occurred. Clinical trial information: NCT04204837. Research Sponsor: Bristol-Myers Squibb.

9529 **Poster Session**

Efficacy of immune checkpoint inhibitor (ICI) rechallenge in advanced melanoma patients responders to a first course of ICI: A multicenter, national, retrospective study of the French group of skin cancers (GCC).

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Background: The efficacy of ICI rechallenge for progressive/recurrent disease of advanced melanoma patients (pts) after a first course of ICI interrupted for disease control has not been systematically described. **Methods:** A retrospective observational multicenter national real-life study evaluated the efficacy and tolerance of ICI rechallenge (anti-PD1, anti-CTLA-4, or combination therapy) in melanoma pts who progressed after disease control with an ICI subsequently interrupted. Primary objective was to evaluate tumor response using RECIST version 1.1. Secondary objectives were the factors associated with tumor response, progression-free survival (PFS), overall survival (OS) and the tolerance of the rechallenge. **Results:** 85 pts from 12 French different centers rechallenged with an ICI between July 2014 and June 2021 were included. Median (IQR) age of pts was 72.00 (30–89) years. Most pts were male (n = 47, 55%) with an AJCC stage IV melanoma (n = 75, 88%). BRAFV600-mutant melanoma and elevated LDH were reported in 19 pts (22%). Pts were rechallenged with anti-PD1 (Pembrolizumab (n = 44, 52%), Nivolumab (n = 35, 41%)), anti-CTLA-4 (Ipilimumab (n = 2, 2%)) or the combination therapy (Ipilimumab + Nivolumab (n = 4, 5%)). Median follow-up after rechallenge was 13 months (1.1-76.2). All pts included had had disease control with the first course of ICI including complete response (CR) in 47 pts (55%), partial response (PR) in 28 pts (33%) and stable disease (SD) in 10 pts (12%). Adverse events (AEs) of the first course of ICI had occurred in 51% pts including grade 3-4 AEs (22%). Median time between ICI interruption and ICI rechallenge was 9,3 months (1.2-63,9). The response rates of ICI rechallenge (2^{nd} course of ICI) were CR in 30 pts (35%), PR in 17 pts (20%) and SD in 17 pts (20%). Progression occurred in 21 pts (25%). The use of steroids for brain metastases was the only factor associated with a higher recurrence rate in multivariate analysis (p = 0,002) and tends to be associated with lower outcomes. There was no correlation between best overall response to the first course of ICI and response to ICI rechallenge. Median duration of response, PFS and OS after ICI rechallenge were not reached. At last follow-up, 23 pts have died. 28 AEs of ICI rechallenge occurred in 23 pts (27%) with a median time of 3 (0.4-36.2) months, including grade 1-2 and grade 3-4 AEs in 13 (15%) and 9 (11%) pts respectively. **Conclusions:** ICI rechallenge for progressive/recurrent disease was associated with high objective response rate (CR+PR = 55%) and disease control rate (CR+PR+SD = 75%) in melanoma pts with a previous disease control induced by ICI. Thus, ICI rechallenge should be considered as an attractive therapeutic option for melanoma pts with progressive/recurrent disease after ICI interruption. Research Sponsor: None.

9530 **Poster Session**

Characterization of patients with metastatic melanoma that relapses following complete metabolic response from anti–PD-1 therapy.

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Background: Treatment with PD-1 inhibitor-based therapy has significantly improved survival in patients with metastatic melanoma over the past decade. Many of these patients achieve complete metabolic response (CMR) by FDG-PET/CT and electively stop treatment. However, the outcomes of patients who relapse after CMR remain uncertain. In this study, we attempt to further characterize metastatic melanoma patients who relapsed following elective discontinuation of anti-PD-1 based therapy due to CMR. **Methods:** We performed a single-center, retrospective analysis on a cohort of patients with metastatic or unresectable melanoma from 2012 to 2021 who were treated with anti-PD-1 monotherapy (pembrolizumab or nivolumab) or combination ipilimumab/nivolumab (I/N), with or without local therapies (surgery or radiation therapy). Patients who achieved a CMR from treatment were identified. CMR was defined as no evidence of metabolically active disease on full-body ^{18}F-FDG-PET/CT and no evidence of new intracranial metastasis on MRI brain. Multiple clinical variables and survival outcomes were assessed. **Results:** Among 386 advanced stage melanoma patients analyzed, 87 achieved a CMR followed by elective treatment cessation with a median anti-PD-1 therapy duration of 10.4 months. 19/87 patients had brain metastasis at baseline. 17/87 patients had disease relapse with a median time to relapse from CMR of 12.1 months. Of those 17 patients, 8 received I/N, 9 received anti-PD-1 monotherapy, and 2 required local therapies to obtain CMR. 7/17 patients were able to achieve CMR again following resumption of anti-PD-1 monotherapy (n = 6) and BRAF/MEK targeted therapy (n = 1). 10/17 patients relapsed in the brain with 7 of those patients having no history of brain metastasis at baseline. Median overall survival after relapse from CMR was 34.1 months. The most common cause of death following relapse from CMR was brain metastasis progression (n = 5). **Conclusions:** A small proportion of metastatic melanoma patients who achieve complete metabolic (CMR) following treatment with anti-PD-1 therapy develop disease relapse. We found that relapse in the brain is common, regardless of baseline involvement at time of therapy, and is a common cause of mortality suggesting the importance of intracranial surveillance following treatment cessation. Ongoing studies are warranted to identify clinicopathologic factors that predict relapse to better inform patients and providers who elect to stop anti-PD-1 therapy. Research Sponsor: None.

9531 **Poster Session**

Progression and mortality post-immunotherapy discontinuation among patients with BRAFV600-mutant (BRAF+) metastatic melanoma.

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Background: Immunotherapy (IO) is commonly used to treat BRAF+ metastatic melanoma (MM) patients in the first line (1L) setting and has demonstrated durable outcomes in clinical trials. However, most patients discontinue IO therapy for toxicity, disease progression, or other reasons. To date, no multi-center or nationwide US-based study has examined treatment patterns and outcomes for patients with BRAF+ MM post discontinuation of 1L IO. The aim of this study is to describe real-world treatment patterns and outcomes among patients who discontinued 1L IO. **Methods:** This retrospective cohort study used the Novartis BRAF+ meLanoma patients ObsErvational (NOBLE) database, the harmonized customized data from Flatiron and ConcertAI. Patients were ≥18 years old, had a diagnosis of BRAF+ MM, were treated with pembrolizumab, nivolumab, or ipilimumab + nivolumab on or after 9/1/2014, and then discontinued 1L therapy. Reason for discontinuation was extracted from medical records. Descriptive statistics were used to describe baseline characteristics and treatment patterns. Kaplan–Meier curves were used to analyze time to progression or death (TTPD) and time to death (TTD). **Results:** Of the 898 included patients (mean age: 61 years; male: 65%); 46% initiated ipilimumab + nivolumab, 24% nivolumab, and 30% pembrolizumab. The most common reasons for 1L discontinuation were toxicity (26%) and progression (25%). Medical records noted 5.3% completed therapy on discontinuation and 34.5% provided no reason of discontinuation with median duration of therapy (MDOT) of 379 and 138 days respectively. At 6 months, 34 % (n = 303) remain on IL IO. MDOT for patients who discontinued IO due to toxicity and those who discontinued due to progression were 54 and 63.5 days respectively. Patients who discontinued due to toxicity had a median time of 142 days to next treatment. TTPD was best for patients who discontinued therapy due to completion or toxicity (6-month progression rate: 13% and 20%). Patients who discontinued due to progression did especially poorly (6-month progression rate: 59%). About 33% of patients (n = 296) needed second line (2L) therapy, and the majority (80.7%) received combination BRAF+ targeted therapy. Overall, 38% and 50% of patients died post IO discontinuation for any reason at 1 and 2 years, respectively. 31% of patients had brain metastases and a greater proportion (56%) died within a 2-year period compared with those without brain metastases (56% vs 49%, p = 0.0036). **Conclusions:** IO, although effective, is not curative for all patients. A significant number of patients discontinue therapy due to progression. Patients with BRAF+ MM who progress early on 1L IO therapy have a high risk of death and should be considered for other therapy options, including targeted therapy. Research Sponsor: Novartis Pharmaceuticals Corporation.

9532 **Poster Session**

Real-world evaluation of the association between baseline metastatic patterns and clinical outcomes among patients with BRAF-positive metastatic melanoma.

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Background: While immunotherapy (IO) and BRAF-targeted therapy (TT) have benefit in BRAFV600 mutant (BRAF+) metastatic melanoma (MM), there is a paucity of real-world data on the impact of systemic therapy choice on outcomes based on key characteristics such as site and number of baseline metastases. Patients with >1 baseline site and certain sites of metastases are also underrepresented or excluded in clinical trials. The aim of this study was to evaluate the association between these characteristics and survival among BRAF+ MM patients. **Methods:** This was a retrospective cohort study using the Novartis BRAF+ meLanoma patients ObsErvational (NOBLE) dataset – harmonized customized data from Flatiron and ConcertAI. It included patients ≥18 years, who received treatment with a first-line (1L) IO (anti-PD-1 mono or combination therapy ipilimumab + nivolumab) or TT (any BRAF/MEK-inhibitors) after 1/1/2014. Progression free survival (PFS) and overall survival (OS) for IO and TT were analyzed according to number (1, 2, 3+ sites) and location (brain, lung, liver, bone) of baseline metastasis. Treatment sequence from 1L to 2L (i.e. IO/TT vs TT/IO) were also compared for PFS and OS outcomes. **Results:** A total of 1,961 patients were included, with 620 patients (32%) on IO monotherapy, 501 patients (26%) on IO combo therapy, and 840 patients (43%) on TT in the 1L. When adjusted for sex, age, ECOG, and Charlson Comorbidity Index, there was no difference in PFS or OS between 1L IO mono, IO combo and TT therapies in patients who had 1, 2, or 3+ baseline metastases. For patients who had either baseline brain, liver, lung, or bone metastasis, there was no difference in PFS and OS between IO mono, IO combo, and TT combo therapies. Of the 521 patients included in the sequencing analysis (only patients who received 2L therapy), 239 patients (46%) had 1L IO/2L TT. There was no difference in PFS or OS between treatment sequences for patients with any number or location of baseline metastasis. **Conclusions:** In this real-world retrospective cohort study, there is no difference in survival between 1L TT and IO for BRAF+ MM patients. Outcomes are comparable regardless of number and location of metastases, including brain metastasis. Whether switching from 1L TT to IO before progression may account for differences compared to trial data will be explored further. Research Sponsor: Novartis Pharmaceuticals Corporation.

Outcomes stratified by number of metastases and metastatic site among patients who received sequencing therapy 1L TT/2L IO.

Reference group: 1L IO/2L TT		PFS		OS	
Number of metastases	**N**	**HR**	**95% CI**	**HR**	**95% CI**
1	165	0.96	0.57 - 1.61	1.51	0.53 – 4.34
2	132	0.56	0.29 - 1.07	0.95	0.22 – 4.03
3+	218	0.75	0.54 – 1.04	1.43	0.60 – 3.38
Metastatic site					
Brain	177	0.82	0.49 – 1.38	1.45	0.41 – 5.14
Liver	150	1.00	0.59 – 1.70	0.57	0.22 – 1.53
Lung	272	0.89	0.61 – 1.29	1.22	0.58 – 2.53
Bone	160	1.24	0.76 – 2.02	1.57	0.59 – 4.17

HR = Hazard ratio; CI = confidence interval.

9533 **Poster Session**

Fecal microbiota transplantation followed by anti–PD-1 treatment in patients with advanced melanoma.

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Background: The gut microbiome has been shown to be a biomarker of response in patients (pts) with melanoma. Strategies to modify the microbiome are currently being investigated. We report the effects of Fecal Microbiota Transplantation (FMT) on safety and anti-PD-1 response in pts with melanoma from a phase I trial (NCT03772899). **Methods:** 20 pts with advanced melanoma with RECIST-evaluable disease, without prior anti-PD-1 treatment for advanced disease, were recruited from 3 Canadian academic centers. Pts with ECOG > 2, autoimmune diseases, immunosuppression or unstable brain metastases were excluded. Pts received 80-100 g of healthy donor stool via oral capsules and were treated with anti-PD-1 one week later. The primary objective was safety of combining FMT with anti-PD-1 therapy. Objective response rate (ORR) by RECIST 1.1 and correlative studies were secondary objectives. Flow cytometry and multiplex ELISA were performed on pts blood samples. Avatar mice were transplanted with stool samples obtained from participants on the trial before and after FMT. Mice were subsequently implanted with B-16 or MCA-205 tumors and received anti-PD-1 antibodies. **Results:** Median age was 75.5 years, 12 (60%) were male, 18 (90%) had stage 4 disease, and 5 (25%) pts harbored a BRAF mutation. Median follow-up was 11.2 months. FMT-related adverse events included grade 2 diarrhea (2 pts) and hypophosphatemia (1 pt), and 13 pts (65%) experienced grade 1 gastrointestinal toxicities. Grade 3 immune-related adverse events (irAE) were one each of myocarditis, nephritis, and fatigue. Anti-PD-1 therapy was discontinued for toxicity in 2 (10%) pts. No unexpected irAE or death on treatment occurred. ORR was 65% (13/20), of which 3 were CR. Clinical benefit rate (includes SD lasting > 6 months) was 75% (15/20). Median PFS was not reached, and one pt died from their disease. Translational analyses demonstrated upregulation of IL-17 post-FMT in responders, which correlated with upregulation of the frequency of Th17 cells in peripheral blood. In parallel, murine experiments showed that feces from pts pre-FMT did not sensitize tumors to anti-PD-1. In both tumor models, only feces obtained post-FMT from responders restored anti-PD-1 efficacy in mice, providing strong support that FMT contributed to the anti-tumor response observed in pts. **Conclusions:** FMT followed by anti-PD-1 treatment in melanoma pts undergoing therapy is safe and may lead to improved anti-tumor responses that can be reproduced in tumor mouse models. The gut microbiome plays an important role in responses to anti-PD-1 in patients with advanced melanoma, paving the way for future microbiome-based interventions. Clinical trial information: NCT03772899. Research Sponsor: Canadian Cancer Society, Lotte & John Hecht Memorial Foundation and the Division of Medical Oncology at London Regional Cancer Program.

9534 **Poster Session**

Outcomes of combined ipilimumab/nivolumab in metastatic uveal melanoma: A prevalence meta-analysis.

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Background: Uveal melanoma is the most common primary intraocular malignant tumor in adults and, approximately 40-50% of the patients eventually develop metastatic disease. Metastatic uveal melanoma has a dismal prognosis with an overall survival of < 50% at 1-year. Single-agent check point inhibitors revealed minimal benefit and novel approaches are underway to improve the outcomes with the recent approval of Tebentafusp in uveal melanoma. The purpose of this metanalysis was to assess the safety and efficacy of combined immunotherapy with ipilimumab (3 mg/kg x q3w for 4 cycles) and nivolumab (1 mg/kg x q3w for 4 cycles) in metastatic uveal melanoma. **Methods:** A comprehensive literature search on PubMed, Embase, Cochrane and Web of Science was conducted. Two independent reviewers screened the literature and extracted data. Our search strategy included MeSH terms and key words for metastatic uveal melanoma; ipilimumab and nivolumab. OpenMeta[Analyst] software was used for the analysis. The endpoints included the prevalence of overall response rate (ORR), complete response (CR), ≥grade-III diarrhea/colitis, and ≥grade-III hepatic toxicity. Additional endpoint included the median overall survival (OS) was reported as a range. Random-effects model (DerSimonian-Laird method) was applied. **Results:** Overall, eight studies (n = 379) were included for the analysis. Five studies were phase II, three studies were retrospective. 52% of the patients were male with good performance status. Median follow-up ranged from 9.2 mo-28 mo. 40% of the patients (n = 142) had elevated LDH at the time of treatment. GNAQ and GNA11 mutations were reported in three studies, BRAF mutation was reported in two studies. The pooled prevalence for ORR was 13.7% (95% CI: 9.2–18.2%, N = 6 studies, n = 33/226) with CR of 2.1% (95% CI: 0.3–3.9%, N = 6 studies, n = 8/226). The median OS ranged from 12.7 to 19.1 months (N = 7 studies). Majority of the patients experienced treatment-related adverse events. Most common side effects included diarrhea, colitis, hepatic toxicities, skin disorders, hypothyroidism. The pooled prevalence for ≥grade III hepatic toxicity was 26.2% (95% CI: 13.9–0.385%, N = 5 studies, n = 60/219). **Conclusions:** Combined checkpoint blockade with ipilimumab and nivolumab showed an ORR of 13.7% which appears to show better clinical activity than single-agent checkpoint inhibitor. Most common treatment side effect was hepatic toxicity. Research Sponsor: None.

9535 **Poster Session**

Phase II study SECOMBIT (sequential combo immuno and target therapy study): A subgroup analysis with a longer follow-up.

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Background: To investigate the best sequential strategy, we started the SECOMBIT study, a randomized three parallel arms phase 2 study (NCT02631447). We used the combination of encorafenib/binimetinib (E+B) as targeted therapy (T-T) and the combination of ipilimumab/nivolumab (I+N) as immunotherapy (I-O). We explored the two different sequences and the "sandwich" strategy with a short course of target therapy, switched by combo immunotherapy at the best response, and not at progression of disease. In our previous report we have observed a trend in favor of the arms where I-O was given as first, confirmed by the first report of the DreamSeq study, a phase III study which compared the two different sequences with T-T and I-O. Here we updated the study data with a subgroup analysis. **Methods:** From Nov 2016 to May 2019, 37 centers in 9 countries enrolled 251 patients with untreated, metastatic *BRAFV600* melanoma. Patients were randomized to Arm A [E+B until PD, followed by I+N], or Arm B (I+N until PD, followed by E+B) or Arm C (E+B for 8 weeks, followed by I+N until PD, followed by E+B). The overall survival (OS) is the primary endpoint of the study. Secondary endpoints included total progression-free survival (tPFS), 2- and 3-years survival rate, best overall response rate, duration of response, biomarkers evaluation. **Results:** The study primary endpoint was met in each arm with at least 30 patients alive at 24 months. The median follow-up estimated with the reverse Kaplan-Meier method was 37.1 months (IQR: 32.8-46.4). The OS at 2 and 3 years was calculated in the three arms for all patients, and in the subgroups normal or elevate LDH level and < 3 or ≥ 3 metastatic sites. OS and tPFS rates at 2 and 3 years are shown in the table. **Conclusions:** With a 37.1 months median follow-up, 2 and 3-years OS as well as tPFS rates are higher in Arm B and C. In line with recent findings, the SECOMBIT results confirm a better trend in favor of Arm B and C treatment sequence. The analysis of the secondary endpoints is ongoing. Clinical trial information: NCT02631447. Research Sponsor: BMS and Array Biopharma/Pfizer.

	2-year tPFS	3-year tPFS	2-year OS	3-year OS	2-year OS < 3ms	3-year OS < 3ms	2-year OS ≥ 3ms	3-year OS ≥ 3ms	2-year OS nLDH	3-year OS nLDH	2-year OS eLDH	3-year OS eLDH
Arm A	44%	34%	62%	53%	70%	62%	50%	36%	73%	67%	50%	42%
Arm B	65%	56%	73%	63%	74%	63%	72%	61%	76%	69%	67%	50%
Arm C	57%	54%	69%	60%	79%	64%	54%	54%	70%	56%	65%	65%

tPFS = time from randomization to second progression; OS = overall survival; ms = no. of metastatic sites; nLDH = normal LDH levels; eLDH = elevated LDH levels.

9536 **Poster Session**

Autoantibodies as potential biomarkers of immune-related adverse events in patients with advanced cutaneous melanoma treated with immune checkpoint inhibitors.

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Background: The majority of patients treated with immune checkpoint inhibitors (ICIs) develop immune-related adverse events (irAE). It is currently not possible to predict the development of irAEs using biomarkers. Here we evaluated the IgG autoantibodies (AAbs) profile in pre-treatment sera of cutaneous metastatic melanoma patients treated with ICIs to identify AAbs that are associated with irAEs. **Methods:** Clinical data of patients with metastatic melanoma treated with pembrolizumab or nivolumab monotherapy (n = 48) or combination ipilimumab and nivolumab (n = 37) was retrospectively evaluated. irAEs were graded using CTCAE v5.0. Sera from the 85 patients were evaluated for IgG AAbs using the HuProt™ microarray v4.0 covering 23,059 proteins (> 81% of the human proteome). AAb profiles were compared between groups (any irAEs vs no irAEs), using the no irAEs group as control group. Results were inputted into the Advaita Bio's iPathwayGuide software to find significantly differentially expressed AAbs using $p < 0.05$ and $Log2FC > 0.6$, and identify relevant biological pathways. **Results:** Out of 85 patients, 60 experienced any grade irAEs, 29 of 48 (60.4%) in the PD-1 group and 31 of 37 (83.8%) in the combination group. We found 758 proteins were differentially elevated, 102 in the in the PD-1 group and 666 in the combination treatment group. A comparison of these groups identified 10 AAbs that were elevated in patients experiencing irAEs independent of ICI regimen. These targeted proteins are highly expressed in tissues that are commonly affected by irAEs. Previous studies have shown their links to autoimmune and inflammatory conditions such as dermatitis and thyroiditis. Pathway analysis shows the RIG like receptor signalling pathway, which has been associated with autoinflammatory conditions, was significantly affected in the PD-1 group ($p = 0.011$), but not in the combination group ($p = 0.442$). Other pathways involved included the NOD-like receptor, purine and D-amino acid metabolism which play a role in innate immune system and assembly of inflammasomes and maturation, pro-inflammatory cytokines and mediators that contribute to inflammatory response. **Conclusions:** Further analyses are being conducted to identify the correlation of irAE type and severity to specific autoantibodies which will be presented. Prospective studies are required for validation of these AAbs specificities. This approach could be used to identify patients at high risk of irAEs, for treatment monitoring to maintain an effective stimulation of the patient's anti-cancer immune response, to determine if treatment cessation is required and prevent hospitalisation or lengthy immunosuppression to treat irAEs. Research Sponsor: Western Australia Cancer and Palliative Care Network.

9537 **Poster Session**

Efficacy and safety of cosibelimab, an anti–PD-L1 antibody, in patients with metastatic cutaneous squamous cell carcinoma.

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Background: Programmed death receptor-1 (PD-1)–blocking antibodies are approved as monotherapy treatment for patients (pts) with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or radiation. Cosibelimab is a high-affinity, fully human programmed death ligand-1 (PD-L1)–blocking antibody with a functional Fc domain capable of inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) against tumor cells. Study CK-301-101 (NCT03212404) is a global, multicenter, multicohort, pivotal trial that enrolled pts with select advanced cancers for treatment with cosibelimab. Here we present the primary analysis of the registration-enabling expansion cohort in pts with metastatic CSCC. **Methods:** Adult pts with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who had metastatic (nodal and/or distant) CSCC not amenable to local therapy were eligible to participate. Cosibelimab was administered as a fixed dose of 800 mg every 2 weeks (Q2W) intravenously. The primary endpoint was confirmed objective response rate (ORR; complete response [CR] + partial response [PR]) assessed by independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and the key secondary endpoint was duration of response. **Results:** Seventy-eight pts with metastatic CSCC were treated with cosibelimab and comprise the efficacy and safety populations (59M/19F; median age: 71 years). The confirmed ORR was 47.4% (95% CI: 36.0, 59.1; 6 CRs and 31 PRs) and the median duration of response was not reached at the time of data cutoff (median duration of follow-up: 15.2 months), with 76% of responses ongoing (range: 1.4-31.8+ months). The Kaplan–Meier estimated probability of maintaining a response at 6 and 24 months was 88.1% and 72.5%, respectively. Treatment-related adverse events (TRAEs) were reported in 54 pts (69.2%); 7 pts (9.0%) experienced at least 1 grade 3 TRAE (no grade 4 or grade 5 TRAEs were reported) with the most common being increased serum lipase in 2 pts. **Conclusions:** Treatment with cosibelimab monotherapy resulted in a robust ORR with durable responses and demonstrated a predictable and manageable safety profile in pts with metastatic CSCC, supporting its use in the treatment of this cancer. Clinical trial information: NCT03212404. Research Sponsor: Checkpoint Therapeutics.

9538 **Poster Session**

Anti-LAG-3 antibody LBL-007 in combination with toripalimab in patients with unresectable or metastatic melanoma: A phase I, open-label, multicenter, dose escalation/expansion study.

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Background: LBL007 is a novel, fully human IgG4 monoclonal antibody targeting human Lymphocyte-activation gene3 (LAG-3). Dual inhibition of anti-programmed cell death protein 1 (PD-1) and LAG-3 is anticipated to synergistically increase immune response against tumor growth. Here we report the preliminary safety and efficacy of LBL-007 in combination with Toripalimab (an anti-PD-1 antibody has approved for treatment of melanoma in China) in patients (pts) with unresectable or metastatic melanoma. **Methods:** Pts with unresectable or metastatic melanoma with or without prior anti-PD-(L)1 therapy were enrolled. This trial comprised 2 parts, namely part 1 (dose escalation), pts received LBL-007 (0.25/1/3/6 mg/kg) /Toripalimab (3 mg/kg) both i.v., Q2W; and part 2 (expansion), pts received LBL-007 (3/6 mg/kg)/Toripalimab (3 mg/kg) both i.v., Q2W. The primary objective was safety, the second objectives included pharmacokinetics, pharmacodynamics and efficacy (per RECIST 1.1). **Results:** By Jan 2022, 37 pts (15 [40.5%] male, median age 59 [range 31-74] years, 9 pts [24.3%] with baseline LDH elevation, 18 [48.6%] with acral, 12 [32.4%] mucosal, 5 [13.5%] nonacral cutaneous, 2 [5.4%] primary site unknown) were enrolled, with 17 in part 1 and 20 in part 2. No dose-limiting toxicity was observed in part 1, and the MTD was not reached. Of all 37 pts, the most common treatment-emergent adverse events (TEAEs) included anemia (24.3%), creatine phosphokinase elevation (24.3%), hypothyroidism (21.6%), and aspartate aminotransferase elevation (21.6%). For 32 radiologically evaluable pts, ORR was 12.5%, DCR was 53.1%. In a preplanned subtype-specific analysis in anti-PD-(L)1 treatment-naïve pts, ORR was 27.3 % vs. 0%, and DCR was 81.8% vs. 50.0% in acral and mucosal melanoma subtypes, respectively. For anti-PD-(L)1-resistant pts (n = 11), DCR was 18.2%. **Conclusions:** LBL007/Toripalimab combination is well tolerated and promising efficacy in pts with unresectable or metastatic melanoma, especially in the acral type without prior anti-PD-(L)1 therapy. Clinical trial information: NCT04640545. Research Sponsor: Nanjing Leads Biolabs Co.,Ltd.

9539 **Poster Session**

The interferon-gamma (IFN-y) signature from baseline tumor material predicts pathologic response after neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) in stage III melanoma.

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Background: Neoadjuvant IPI + NIVO induces high pathologic response rates (pRR) of 74-78% in macroscopic stage III melanoma. Pathologic response (< 50% viable tumor) is strongly associated with improved relapse-free survival (RFS); the previous OpACIN-neo study demonstrated a 2-year RFS of 96.9% in patients (pts) with pathologic response, whereas the 2-year RFS in non-responders was 35.5%. These data highlight the need for baseline biomarkers predictive for response and survival. Here, we present the predictive value of the 10-gene IFN-y expression signature algorithm (based on Ayers et al.) for pathologic response and relapse in a cohort of melanoma pts treated with neoadjuvant IPI + NIVO. **Methods:** Baseline tumor biopsies from lymph node metastases of stage III melanoma pts were used for IFN-y signature assessment. Pts were treated with a maximum of two cycles of neoadjuvant IPI 1mg/kg + NIVO 3mg/kg in the OpACIN-neo (arm B) and PRADO studies. RNA expression analysis was conducted using the nCounter® PanCancer Immune Profiling panel on the NanoString Flex machine (NanoString Technologies), which is clinically applicable due to its fast turn-around-time (two days). An IFN-y signature gene expression score (IFN-y score) was calculated using a NKI-developed algorithm. Association between IFN-y score and pathologic response or event-free survival (EFS) was examined by logistic regression and Cox analyses. The optimal cutoff between a high and low IFN-y score was defined based on a summary receiver operating characteristic (sROC) curve. **Results:** In total, 103 pts treated in the OpACIN-neo and PRADO studies had baseline tumor material available. Median age was 56 years, 62% was male, and 52% had a high baseline IFN-y score. The pRR of the total cohort was 70% (72/103 pts), including 56% (58/103) major pathologic response (MPR, 0-≤10% viable tumor) and 14% (14/103) partial responses (pPR, 10-≤50% viable tumor). 30% (31/103 pts) had no pathologic response. After a median follow-up of 25.2 months, 26 pts (25.2%) developed a melanoma relapse. The IFN-y score was significantly associated with response (OR 1.061, $p < 0.001$) and relapse (OR 0. 974, $p = 0.029$). The pRR was 89% (48/54) in pts with a high IFN-y score versus 49% (24/49) in those with a low IFN-y score ($p < 0.001$). Pts with a high IFN-y score were also less likely to develop a relapse (11% [6/54] versus 41% [20/49], $p = 0.001$). **Conclusions:** Pts with a high IFN-y score in pre-treatment biopsies are more likely to respond to neoadjuvant IPI + NIVO with favorable EFS. A rapid gene expression analysis enables the IFN-y score to be used in daily clinical practice to identify pts who might qualify for treatment escalation or de-escalation. The DONIMI study [NCT04133948] currently investigates different neoadjuvant treatment combinations in stage III melanoma pts based on their intratumoral IFN-y score. Research Sponsor: None.

9540 **Poster Session**

EMRseq: Registry-based outcome analysis on 1,000 patients with BRAF V600–mutated metastatic melanoma in Europe treated with either immune checkpoint or BRAF-/MEK inhibition.

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Background: In BRAF mutated metastatic melanoma, potential outcome differences for different choices of 1st line treatments including immunotherapy or BRAF-/MEK inhibition are not completely understood. We therefore analyzed the treatment patterns and outcome of systemic therapies for patients BRAF mutated metastatic melanoma. **Methods:** From the EUMelaReg treatment registry, patients fulfilling the following inclusion criteria were consecutively included until a number of 1,000 evaluable cases was reached. 1) Patients with metastatic melanoma and BRAF V600 mutation 2) First line treatment with either combined BRAF-/MEK or immune checkpoint inhibition (ICI) with PD-1 single agent or combined PD-1/CTLA-4 antibodies. Multivariable cox regression analysis as well as propensity score based weighting were used to control for bias from baseline imbalances. Primary outcomes of interest were overall survival (OS) and 2nd line PFS (PFS-2), stratified for upfront treatment decision of ICI versus targeted therapy. PFS-2 was defined as the interval from start of first line treatment to a progression after a 2nd line treatment or death of any cause. Further endpoints were evaluated including time on treatment (ToT), time to next treatment and 2nd line treatments. **Results:** In total 529 (52.9 %) patients received BRAF/MEK-i, and 471 (47.1%) ICI. For various co-variates there were significant imbalances between strata, including number of metastatic sites, AJCC substage, serum LDH, and ECOG performance status, with more favorable prognostic variables for patients receiving immunotherapy. The ORR for BRAF/MEK-i was significantly higher than for ICI (53.3% vs. 42.0%; p=0.0004), but for OS and PFS2 the adjusted hazard ratios were significantly in favor for ICI (HR 0.62 and 0.66, respectively; p <0.0001). In 2nd line, patients switching from ICI to BRAF/MEK-i had again markedly higher ORR than patients switching vice versa (57.7% vs. 19.9%; P<0.0001), and also significantly longer unadjusted PFS (8.1 vs. 3.1 months; p <0.0001) and OS (15.7 vs. 10.6 mths; p=0.01) after start of 2nd line treatment. **Conclusions:** The two cohorts had imbalances on key prognosis variables. After adjustment for these imbalances, upfront ICI still resulted in significantly longer OS as compared to BRAF/MEK-i. Due to the nature of real-world observational data causing inherent imbalances in the treatments cohorts and being unable to account for potential unknown confounders, outcome may still be biased despite adjustment efforts. Research Sponsor: None.

	1st line Therapy		
	BRAFi+MEKi (N = 529)	ICI (N = 471)	P value
Objective Remissions	282 (53.3%)	198 (42.0%)	0.0004
Median PFS2 [m] (95% CI)*	12.3 (11.3-14.8)	21.9 (17.6-33.0)	< 0.0001
Median OS [m] (95% CI)*	16.9 (15.2-22.3)	45.0 (30.2-NA)	< 0.0001

*Adjusted by inverse propensity score weighting for confounding factors.

9541 **Poster Session**

Meta-analysis of randomized phase II-III trials evaluating triplet combinations of immunotherapy and targeted therapy for BRAF V600-mutant unresectable or metastatic melanoma.

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Background: Immune-checkpoint inhibitors (ICI) and targeted-therapies (TT) have become standard options for BRAF -V600 metastatic melanoma (B-mut MM) patients. However, still more than 50% of those patients do not respond or relapse to these current strategies. Preclinical and translational data suggest that ICI plus TT may improve treatment outcomes in patients with B-mut MM, but with conflicting results in the clinical setting. **Methods:** We performed a systematic review and meta-analysis of randomized phase II-III studies published until January 2022 comparing first-line ICI+TT vs TT alone in B-mut MM. We obtained summary estimates through random-effects models. Overall survival (OS) and progression-free survival (PFS) were the main outcomes retrieved but we look also at difference in responses and adverse events. **Results:** We summarized data from 3 independent trials and we showed a significant advantage in terms of PFS and OS for the experimental arms in B-mut MM patients treated with ICI+TT rather than TT alone. The summary estimate indicates a significant 23% decrease in risk of progression (SHR = 0.77, 95%CI: 0.66-0.89, with no between-study heterogeneity I^2= 0%) and a significant 21% reduction in risk of death (SHR = 0.79, 95%CI: 0.66-0.96, with no heterogeneity I^2= 0%). However, no difference was shown (p-value = 0.56) between arms in terms of summary Objective Response Rate (ORR) estimates (Summary ORR doublet = 65.4% [61.5%; 69.2%] and Summary ORR triplet = 67% [63%; 70.9%], respectively). From the subgroup analysis on PFS risk estimates, no significant differences were observed in summary HRs by age (< 65 vs ≥65 years, p-value = 0.11), sex (female vs male, p-value = 0.58), ECOG PS (0 vs 1, p-value = 0.36), LDH levels (lower vs upper, p-value = 0.59) and PDL1 status (positive vs negative, p-value = 0.89). Significant differences were found in frequencies of grade 3 or more adverse events with higher number of events occurring in B-mut MM vs TT alone (Summary Odd Ratio = 2.01, 95%CI: 1.16-3.47, I^2= 74%), whereas no significant differences were found in terms of any adverse event between arms (SOR = 1.83, 95%CI: 0.70-4.78, I^2= 0%). **Conclusions:** This study supports and extend the discussion on first-line available combinations to be offered to B-mut MM patients. Combining ICI with TT demonstrated an effective advantage on both PFS and OS, although augmenting toxicities. Further biomarker-driven investigation may identify patient subpopulations who could benefit from ICI+TT combinations in order to expand their window of therapeutic opportunities. Research Sponsor: None.

9542 **Poster Session**

The prognostic impact of immune-related adverse events in real-world patients with metastatic melanoma treated with single-agent and combination immune checkpoint blockade.

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Background: Immune checkpoint blockade (ICB) has revolutionized the treatment of metastatic melanoma (MM). Immune-related Adverse Events (irAEs) associated with ICB have been shown to correlate positively with survival outcomes across solid tumours. In MM, conclusions on the impact of irAE severity have been conflicting, and combination ICB therapy experience is limited to smaller cohorts. We sought to clarify these relationships using the Alberta Immunotherapy Database (AID). **Methods:** The AID provides a multi-centre, province-wide observational cohort comprising consecutive patients treated with ICB. We included adult patients with MM, treated with ICB (single agent nivolumab or pembrolizumab, or combination ipilimumab and nivolumab) at any line of therapy, agnostic to site of origin, from August 2013 to May 2020, with analysis in December 2021. The primary endpoint of interest was the identification of a relationship between development of irAEs and subsequent overall survival (OS, defined from time of ICB initiation). To minimize immortal time bias from poor prognosis patients who may have died prior to the development of irAEs, patients who died before 12 weeks were excluded from OS and time-to-next-treatment (TTNT) analysis. Adjusted Cox regression analyses were performed to determine the association of variables with OS. **Results:** Of 492 MM patients receiving ICB, 124 received combination ICB, 198 developed an irAE and 67 required hospitalization for an irAE. irAEs were more common in patients < 50 years old ($p = 0.02$), with ECOG 0 ($p < 0.001$) and normal albumin ($p = 0.002$). Median time to irAE development (2.6 months) and frequency of individual irAEs were consistent with the published literature. In the overall population, patients who experienced an irAE had longer median OS (56.3 vs 18.5mo, $p < 0.0001$), and TTNT (49.6 vs 12.9mo, $p < 0.0001$). This remained consistent in combination ICB-treated patients (median OS 56.3 vs 19mo, $p < 0.0001$). Patients hospitalized for an irAE had improved OS and TTNT over patients requiring only outpatient treatment (median OS NR vs 27.9mo, $p = 0.0039$), while ICB re-challenge after an irAE also improved OS (56.3 vs 31.5mo, $p = 0.0093$). Development of an irAE retained independent association with OS after adjusted multivariable regression (HR 0.376, $p < 0.001$). **Conclusions:** These data support the association of irAEs and improved survival outcomes in MM, including those patients treated with combination ICB. Among patients with irAE, hospitalization for irAE, and ICB re-challenge post-irAE, were further associated with improved outcomes. Research Sponsor: None.

9543 **Poster Session**

Metabolic complete responses (mCR) in patients with metastatic uveal melanoma (mUM) treated with image-guided injection (IGI) of PV-10.

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Background: Traditional CT imaging can underestimate the degree of anti-cancer treatment effect due to reliance on morphological changes of visualized tumors. In contrast, PET imaging offers information on metabolic activity using a positron emitting radiolabeled agent (e.g. FDG) but is less sensitive to changes in tumor size. FDG-PET images acquired, co-registered, and superimposed on CT images (PET-CT) allow spatial detection of anti-cancer activity. Moreoever, FDG-PET-CT can provide information regarding anti-tumor immune responses in patients receiving immunotherapy. Rose bengal (PV-10) is a small molecule autolytic immunotherapy in development for metastatic disease. When administered by intralesional injection, PV-10 can produce immunogenic cell death and a T-cell mediated immune response against treatment-refractory and immunologically-cold tumors. Herein, we report the FDG-PET-CT imaging responses of 7 metastatic uveal melanoma (mUM) patients who received percutaneous image-guided injection (IGI) of PV-10 into hepatic tumors. **Methods:** The Phase 1 study is evaluating safety, tolerability, and efficacy of intralesional PV-10 in hepatic tumors. PV-10 is administered percutaneously via IGI into designated tumors ≤4.9 cm in diameter. Response is assessed at Day 28, then every 3 months, using CT/MRI or PET-CT. Patients with multiple tumors may receive further IGI of PV-10 after Day 28. **Results:** To date, 25 mUM patients with liver metastases have been treated; 16 patients received standard of care immune checkpoint inhibitor (ICI) during or post PV-10 treatment. Seven subjects had FDG-PET-CT imaging during the study (baseline 1, follow-up 6). Two follow-up FDG-PET-CTs were performed 1 and 3 years after PV-10 injection with intervening ICI, and another was 1.5 years after PV-10, without any follow-on treatment. Four patients experienced mCR in all metastatic sites, including extrahepatic metastasis. **Conclusions:** FDG-PET-CT shows that PV-10 is capable of inducing mCR in injected (adscopal) and non-injected (abscopal) lesions. This pattern of response is suggestive of immunogenic cell death in mUM patients with liver metastases. Clinical trial information: NCT00986661. Research Sponsor: Provectus Biopharmaceuticals.

9544 **Poster Session**

Better (a little) late than never: The impact of steroidal treatment initiation timing on the outcome of patients with melanoma treated with immunotherapy.

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Background: The immune-system manipulation by immune-checkpoint inhibitors (ICI) has led to unprecedented clinical advances in melanoma. The management of the consequent immune-related adverse events (irAEs) is based mostly on steroids and other immune-modulators. **Methods:** A real world single-site cohort of metastatic melanoma patients who were treated with immunotherapy as first line between 2014 and 2020. This study explores the effect of dose, timing, and duration of steroid exposure on treatment efficacy. **Results:** Four hundred and forty patients were treated with either anti PD-1 (n = 285, 65%) or combination of anti PD-1 and ipilimumab ICI (n = 112, 25%), or ipilimumab alone (n = 43, 10%). The median age was 68 years [12-99y], and 57% were male. Any-grade irAEs were seen in 71% of the patients, and 49% were exposed to steroids. The median steroid dose was 0.75mg/kg prednisolone equivalent [0.03- 80mg/kg], the median duration of steroidal treatment was 11.2 weeks [0.1-316w] and the median time to onset of steroids was 7.6 weeks [0-193w]. Both experiencing irAEs, and the associated steroid exposure were associated with a significant progression free survival (PFS) benefit [HR 0.47, $p < 0.001$; 95%CI 0.39-0.6 and HR 0.77, $p = 0.026$; 95%CI 0.60-0.97, respectively], regardless of dose and duration. Notably, within those who were exposed to steroids, an earlier onset of < 4 weeks from immunotherapy initiation was significantly associated with a shorter PFS [HR = 3.5, $p < 0.001$ (95%CI 2.32-5.45)]. This observation resulted significant also on multivariable analysis including other prognostic variables – ECOG PS, M-stage, LDH and protocol. **Conclusions:** Steroidal treatment during the immunotherapy priming phase (first 4 weeks) might have a deleterious effect on its' efficacy and should be explored in larger prospective cohorts. Research Sponsor: None.

9545 **Poster Session**

Glycoproteomics as a powerful liquid biopsy-based predictor of checkpoint inhibitor treatment benefit in metastatic malignant melanoma.

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Background: Protein glycosylation is the most abundant and complex form of post-translational protein modification. Glycosylation profoundly affects protein structure, conformation, and function. The elucidation of the potential role of differential protein glycosylation as biomarkers has so far been limited by the technical complexity of generating and interpreting this information. We have recently established a novel, powerful platform that combines liquid chromatography/mass spectrometry with a proprietary artificial-intelligence-based data processing engine that allows, for the first time highly scalable interrogation of the glycoproteome. **Methods:** Using this platform, we interrogated 526 glycopeptide (GP) signatures derived from 75 serum proteins in pretreatment blood samples from a cohort of 205 individuals (66 females, 139 males, age range 24 to 97 years) with metastatic malignant melanoma treated either with nivolumab plus ipilimumab (95 patients) or pembrolizumab (110 patients) immune-checkpoint inhibitor (ICI) therapy. **Results:** In an optimized assay containing 27 glycopeptides and 20 non-glycosylated peptides, we identified 14 GPs with abundance differences at FDR $q \leq 0.05$ with regard to PFS. Using 40% of the cohort as a training set and selecting 12 glycopeptide and non-glycosylated peptide biomarker features of the 47 total by LASSO shrinkage, we created a multivariable-model-based classifier for PFS that yielded a hazard ratio (HR) for prediction of likely ICI benefit of 7.5 at $p < 0.0001$. This classifier was validated in the test set comprised of the held-out 60% of patients, yielding a HR of 4.7 at a similar p-value for separating patients likely benefiting from ICI therapy and those likely not benefiting from ICI therapy (50% PFS of 18 months vs. 3 months based on classifier score above/below cutoff). This classifier has a sensitivity of > 99% to predict likely ICI benefit, while still performing at a specificity of 26%, thus helping to safely reduce ultimately unnecessary and non-beneficial exposure to these agents of one in four who otherwise would unnecessarily be exposed to them. **Conclusions:** Our results indicate that glycoproteomics holds a strong promise as a predictor for checkpoint inhibitor treatment benefit that appears to significantly outperform other currently pursued biomarker approaches in this context. Research Sponsor: None.

9546 **Poster Session**

Management of checkpoint inhibitor toxicity and survival in patients with advanced melanoma.

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Background: Management of checkpoint-inhibitor-induced immune-related adverse events (irAEs) is primarily based on expert opinion. Recent studies have suggested detrimental effects of immunosuppressive treatment with anti-TNF on checkpoint-inhibitor efficacy. **Methods:** Advanced melanoma patients experiencing grade ≥3 irAEs after treatment with first-line ipilimumab-nivolumab between 2015 and 2021 were included from the Dutch Melanoma Treatment Registry. Progression-free survival (PFS), overall survival (OS) and melanoma-specific survival (MSS) were analyzed according to toxicity management regimen. A cox proportional hazards model was used to account for the confounders age, sex, performance status, lactate dehydrogenase, site of metastases and type of irAE. **Results:** Out of 771 ipilimumab-nivolumab treated patients, 350 were treated with immunosuppression for severe irAEs. Of these patients, 235 received steroids only and 115 received steroids with second-line immunosuppressants consisting of anti-TNF, mycophenolic acid, tacrolimus and other immunosuppressants. Median PFS was significantly longer for patients treated with steroids (11.3 months) than for patients treated with steroids and second-line immunosuppressants (5.4 months; HR 1.43; 95%CI 1.07-1.90; p = 0.01). Median OS was also significantly longer for the steroids group (46.1 months) than for the steroids and second-line immunosuppressants group (22.5 months; HR 1.64; 95%CI 1.16-2.32; p = 0.005). Results for MSS were similar (not reached versus 28.8 months; HR 1.70; 95%CI 1.16-2.49; p = 0.006). Median PFS, OS and MSS are shown in Table 1. After adjustment for potential confounders, patients treated with steroids + second-line immunosuppressants showed a non-significant trend towards a higher risk of progression (HR_{adj} 1.40; 95%CI 1.00-1.97; p = 0.05), a higher risk of death (HR_{adj} 1.54; 95%CI 1.03-2.30; p = 0.04) and of melanoma-specific death (HR_{adj} 1.62; 95%CI 1.04-2.51; p = 0.032) compared to the steroids group. **Conclusions:** Second-line immunosuppression for irAEs is associated with impaired PFS, OS, and MSS in advanced melanoma patients treated with first-line ipilimumab-nivolumab, irrespective of being anti-TNF or other second-line immunosuppressants. These findings stress the importance of assessing the effects of differential irAE management strategies, not only in melanoma but also in other tumor types. Research Sponsor: The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002).

	Median PFS mo (95% CI)	P-value*	Median OS mo (95% CI)	P-value*	Median MSS mo (95% CI)	P-value*
Steroids (n = 235)	11.3 (9.6 – 19.5)		46.1 (39.0 – NR)		NR(46.1 – NR)	
Steroids + all second-line immunosuppressants (n = 115)	5.4 (4.5 – 12.4)	0.014	22.5 (36.5 – NR)	0.005	28.8 (20.5 – NR) 0.0	0.006
Steroids + anti-TNF (n = 67)	5.4 (4.7 – 13.1)	0.034	28.7 (12.2 – NR)	0.019	31.7 (15.7 – NR)	0.033
Steroids + other second-line immunosuppressants (n = 35)	4.3 (2.5 – 13.2)	0.025	22.4 (13.2 – NR)	0.084	22.4 (13.2 – NR)	0.024

*Compared to steroids group.

9547 **Poster Session**

Overall survival (OS) with first-line atezolizumab (A) or placebo (P) in combination with vemurafenib (V) and cobimetinib (C) in *BRAF*^{V600} mutation-positive advanced melanoma: Second interim OS analysis of the phase 3 IMspire150 study.

Grant A. McArthur, Ralf Gutzmer, Daniil Stroyakovskiy, Helen Gogas, Caroline Robert, Svetlana Protsenko, Rodrigo Perez Pereira, Thomas Eigentler, Piotr Rutkowski, Lev V. Demidov, Natalia V. Zhukova, Jacob Schachter, Yibing Yan, Ivor Caro, Christian Hertig, Cloris Xue, Lieke Kusters, Paolo Antonio Ascierto, Karl D. Lewis; Melanoma and Skin Service and Cancer Biology and Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Dermatology, Mühlenkreiskliniken, Ruhr University Bochum Campus, Minden, Germany; Moscow City Oncology Hospital #62 of Moscow Healthcare Department, Moscow, Russian Federation; First Department of Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, Athens, Greece; Gustave Roussy and Paris-Saclay University, Villejuif-Paris, France; Department of Chemotherapy and Innovative Technologies, N. N. Petrov National Medical Research Center of Oncology, St Petersburg, Russian Federation; Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Dermatology, Venereology and Allergology, Berlin, Germany; Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; N.N.Blokhin NMRC of Oncology MoH of Russia, Moscow, Russian Federation; St. Petersburg State University, St. Petersburg, Russian Federation; Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Ramat-Gan, Israel; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd., Basel, Switzerland; Hoffmann-La Roche Canada Ltd., Mississauga, ON, Canada; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; University of Colorado Comprehensive Cancer Center, Aurora, CO

Background: Primary analysis of the phase 3 IMspire150 study (NCT02908672) demonstrated improved investigator-assessed progression-free survival (PFS) with first-line A + V + C vs P + V + C in patients (pts) with *BRAF*^{V600} mutation–positive advanced melanoma (hazard ratio [HR] 0.78; 95% CI, 0.63-0.97; *P*= 0.025). With median follow-up of 18.9 months at primary analysis, OS data were immature; interim analysis of OS at the time of the primary analysis demonstrated a trend in favor of A + V + C over P + V + C (estimated 2-year OS rate, 60.4% vs 53.1%) (Gutzmer et al. *Lancet* 2020;395:1835-1844). Herein, we present results from the second interim OS analysis of the IMspire150 study. **Methods:** IMspire150 enrolled previously untreated pts with stage IV or unresectable stage IIIc *BRAF*^{V600} mutation-positive melanoma (n = 514). Pts were randomized 1:1 to receive 28-day cycles of A + V + C (n = 256) or P + V + C (n = 258). Pts received V + C in cycle 1; A or P was added on days 1 and 15 from cycle 2 onwards. The second interim OS analysis was planned after ~270 OS events were recorded, and was projected to have a minimally detectable difference of HR of 0.74 with a *P* value boundary of 0.0140. OS was estimated using the Kaplan-Meier method. **Results:** At data cutoff (Sept 8, 2021), 273 OS events had occurred. Median follow-up was 29.1 months (range, 1-54) for A + V + C and 22.8 months (range, 0-54) for P + V + C. A continued trend toward OS benefit in favor of A + V + C over P + V + C was observed with median OS of 39.0 vs 25.8 months, but the difference did not reach statistical significance (HR, 0.84; 95% CI, 0.66-1.06; *P*= 0.1432). A delayed treatment effect was observed, with landmark OS rates for A + V + C vs P + V + C of 76.1% vs 76.5% at 12 months and 61.5% vs 53.3% at 24 months. With additional follow-up, A + V + C continued to show PFS benefit over P + V + C (HR, 0.79; 95% CI, 0.64-0.97; *P*= 0.0224); overall response rates (66.7% vs 65.0%) and median duration of response (21.0 vs 12.6 months) remained consistent with those reported at primary analysis. No new safety signals were observed with additional follow-up. **Conclusions:** With further follow-up, A + V + C demonstrated a consistent, but not statistically significant, improvement in OS and continued benefit in duration of response versus P + V + C in previously untreated pts with *BRAF*^{V600} mutation–positive advanced melanoma. Clinical trial information: NCT02908672. Research Sponsor: This study and medical writing and editorial support for this abstract was funded by F. Hoffmann-La Roche Ltd.

9548 **Poster Session**

Efficacy and safety of sequencing with vemurafenib (V) plus cobimetinib (C) followed by atezolizumab (Atezo) in patients (pts) with advanced *BRAF*^{V600}-positive melanoma: Interim analysis of the ImmunoCobiVem study.

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Background: Immunotherapies (ICI) and targeted therapies (TT) have improved PFS and OS in *BRAF*^{V600}-mutated advanced melanoma pts, but evidence regarding their optimal sequence is limited. The randomized phase 2 ImmunoCobiVem study evaluated efficacy and safety of an early switch to Atezo after initial treatment with V + C. Interim results are reported. **Methods:** Pts with previously untreated *BRAF*^{V600}-mutated advanced melanoma received a 3-mo run-in with V (960 mg twice daily) + C (60 mg once daily for 21/28 days). Pts without PD/treatment interruption due to AEs during run-in were then randomized 1:1 to continue V + C (Arm A) or switch to Atezo (1200 mg every 3 wks; Arm B) until first documented PD (PD1), followed by crossover to the alternate treatment until second documented PD (PD2). End points were PFS1 (time from start of run-in until PD1 or death from any cause), PFS2 (time from start of run-in until PD2 or death from any cause), PFS3 (time from PD1 until PD2 or death from any cause), DCR, ORR, OS, and safety. **Results:** 185 pts were enrolled between Nov 2016 and Dec 2019 (63% male; median age 58 y); 135 pts completed run-in and were randomized to Arm A (n=69) or Arm B (n=66). At data cutoff, median follow-up for all pts was 19.0 mo. In Arm A, 36/69 pts (52%) discontinued V + C due to PD and 21/36 (58%) crossed over to Atezo; in Arm B, 49/66 pts (74%) discontinued Atezo due to PD and 35/49 (71%) crossed over to V + C. Median PFS1 was significantly longer in Arm A vs Arm B (HR 0.55; 95% CI 0.37–0.84; *P*=0.001), while median PFS3 was significantly shorter in Arm A vs Arm B (HR 2.24; 95% CI 1.17–4.30; *P*=0.013); median PFS2 was not significantly different between arms (HR 1.57; 95% CI 0.83–2.96; *P*=0.163) (Table). During the randomized phase, ORR and DCR were higher in Arm A before crossover and in Arm B after crossover (Table). OS was similar between arms (HR 1.22; 95% CI 0.69–2.16; *P*=0.389). Median (range) treatment duration across treatment phases was 11.2 mo (2.3–56.1) for Arm A and 10.7 mo (2.8–56.7) for Arm B. Grade 3/4 AEs occurred in 55% of pts in Arm A and 64% in Arm B; AEs led to discontinuation in 10% and 12%, respectively. **Conclusions:** Early switch from V + C to Atezo is feasible and safe, but tumor control achieved in run-in is maintained in only a subset of pts on subsequent ICI monotherapy. Crossover to ICI monotherapy at PD results in low response, while response to TT re-exposure is frequent. Clinical trial information: NCT02902029. Research Sponsor: This study and medical writing and editorial support for this abstract was funded by F. Hoffmann-La Roche Ltd.

	Arm A		Arm B	
PFS	**Events/pts**	**Median, mo(95% CI)**	**Events/pts**	**Median, mo(95% CI)**
PFS1	42/67	13.9 (9.9–16.6)	51/65	5.9 (5.4–8.3)
PFS2	18/21	12.6 (8.3–17.0)	21/35	14.9 (8.6–25.6)
PFS3	18/21	2.8 (2.0–3.1)	21/35	6.0 (2.4–12.6)
Response, % (95% CI)	ORR	DCR	ORR	DCR
Run-in phase	74 (62–83)	99 (92–100)	74 (63–83)	98 (92–100)
Randomized phase				
Before crossover	67 (55–77)	72 (61–82)	36 (26–48)	42 (31–54)
After crossover	5 (1–23)	10 (3–29)	40 (26–56)	54 (38–70)

9549 **Poster Session**

Merkel polyoma virus specific T-cell receptor transgenic T-cell therapy in PD-1 inhibitor refractory Merkel cell carcinoma.

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Background: Merkel cell carcinoma is an aggressive neuroendocrine tumor of skin origin with most cases caused by the Merkel polyoma virus (MCPyV). While many patients benefit from PD-1/PD-L1 axis blockade, most patients do not respond or develop resistance. We sought to ask whether adoptive transfer of autologous T cells transduced with MCPyV specific T cells could lead to clinical responses in PD-1 inhibitor refractory patients. **Methods:** Five MCPyV positive, HLA-A02 patients with PD-1 inhibitor refractory metastatic Merkel cell carcinoma were treated with adoptive transfer of CD62L+ CD8+ and CD4+ autologous T cells transduced with a T cell receptor (TCR) targeting an HLA-A0201 restricted MCPyV epitope. Two different strategies were used to facilitate T cell expansion: In 3 patients, single fraction radiation was administered to a subset of lesions prior to T cell transfer. In 2 patients, lymphodepleting chemotherapy with cyclophosphamide and fludarabine was administered prior to T cell transfer. Anti PD-1/PD-L1 therapy was given 14 days after T cell infusion. Transgenic T cells were visualized in tumor biopsies by multiplex immunohistochemistry. **Results:** 5 patients were treated, with 4 patients receiving 100 million tetramer positive CD8+ T cells and one patient receiving 500 million cells. 3 patients received second infusions with between 300 million and 900 million tetramer positive cells. No dose limiting toxicities or cytokine release syndrome were observed. T cell persistence was lower in the 2 patients treated with lymphodepleting chemotherapy relative to the 3 patients treated with single fraction radiation. Transgenic T cells persisted at tumor sites greater than 1 month following transfer. 4 patients experienced progressive disease, and a single patient had a mixed response and greater than 1 year disease free interval following local therapy of an isolated site of progression. The responding patient was the only patient with class I MHC staining on tumor cells prior to treatment, and the site of local progression in that patient showed the presence of TCR transgenic T cells but loss of class I MHC expression. **Conclusions:** MCPyV specific transgenic T cells are safe, traffic to tumor sites, and can result in a clinical response, but their clinical activity may be limited by down-regulation of class I MHC expression on tumors. A future trial will address strategies to increase class I MHC expression on Merkel tumors. Clinical trial information: NCT03747484. Research Sponsor: Bluebird, Other Government Agency.

9550 **Poster Session**

Camrelizumab plus apatinib for patients with advanced mucosal melanoma: A prospective single-arm study.

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Background: Mucosal melanoma is a rare subtype in white populations, but the second most common subtype in Asian populations. This subtype is a more aggressive malignancy, with high risk of metastasis and death. Immune checkpoint inhibitor combined with anti-angiogenic agent has been investigated in many solid tumors, including some preliminary evidence (NCT03086174 and NCT04091217) in Chinese patients with advanced mucosal melanoma. This study investigated the efficacy and safety of camrelizumab plus apatinib in patients with advanced mucosal melanoma. **Methods:** In this prospective, single-arm study (ChiCTR1900023277), patients with inoperable stage III-IV or recurrent/metastatic mucosal melanoma and Eastern Cooperative Oncology Group performance status of 0-1 were enrolled. Patients received camrelizumab 200 mg once every 2 weeks and apatinib 500 mg once daily until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) according to the Response Evaluation Criteria In Solid Tumors, version 1.1. **Results:** Between April 2019 and January 2022, a total of 30 patients were enrolled (Table). As of January 2022, 21 patients had at least one efficacy assessment, and the median follow-up duration was 8.1 months. The ORR was 42.9%, including one (4.8%) patient with confirmed complete response, six (28.6%) with confirmed partial response (PR), and two (9.5%) with unconfirmed PR. The disease control rate (DCR) was 81.0%. The median progression-free survival was 7.2 months (95%CI, 5.8-not reached [NR]) in 21 patients, 7.7 months (95%CI, 5.8-NR) in 19 patients with first-line camrelizumab plus apatinib treatment, and 9.8 months (95%CI, 4.2-NR) in 11 patients without prior chemotherapy. The most common treatment-related adverse events in 27 patients with available safety data were fatigue (17 [63.0%]), hypertension (15 [55.6%]), and elevated transaminase (14 [51.9%]). No treatment-related deaths occurred. Exploratory analysis found a tendency that patients with high T cell receptor diversity had better prognosis. Higher frequencies of Vβ-Jβ (including Vβ5-8Jβ2-7, Vβ28J2-4 and Vβ12-5Jβ1-1) indicate better survival, and Vβ12-5Jβ1-1 is an independent factor after multivariate adjustment. **Conclusions:** Camrelizumab plus apatinib showed favorable ORR and DCR in patients with advanced mucosal melanoma, with an acceptable safety profile. Follow-up for survival outcomes is ongoing. Clinical trial information: ChiCTR1900023277. Research Sponsor: National Natural Science Foundation of China (No. 81872484 and 82073365), Other Foundation.

Characteristics	Patients (n = 30)
Age (years), median (range)	62 (35-77)
Sex (male/female)	13/17
Current therapy line (1/≥2)	27/3
Prior chemotherapy (perioperative therapy/for advanced disease/no)	12/3/15
Primary site (head and neck/esophagus/vagina and cervix/rectum)	16/2/7/5
Metastatic site (liver/lung/lymph node)	7/11/12
Lactate dehydrogenase level (≤upper limit of normal/ > upper limit of normal)	20/10
Gene mutation (BRAF/C-KIT/NRAS/unknown)	3/3/8/2

9551 **Poster Session**

Analysis of overall survival (OS) and relapse-free-survival (RFS) in the phase 1b clinical trial of anti–PD-1 ab (toripalimab) plus intralesional injection of OrienX010 in stage IV melanoma with liver metastases.

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Background: Advanced melanoma with liver metastasis has reduced response to anti-PD-1 monotherapy with ORR of 4.3% in a pooled analysis, and initial results of the phase 1b trial, systemic toripalimab combined with intrahepatic OrienX010 injection - a HSV-1-derived oncolytic virotherapy with expression of GM-CSF had shown its efficacy. Here we report the RFS and OS outcomes. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extra-hepatic metastasis; the ocular melanoma and brain metastasis were excluded. Pts received intravenous toripalimab Q2W combined with ultrasound guided intratumoral injection of OrienX010 Q2W (8×10^7 pfu/ml, 10ml per injection) until intolerance or disease progression per iRECIST criteria. Liver biopsy would be performed at baseline and first tumor evaluation (8-12weeks). The primary endpoint was toxicity; secondary endpoints included ORR, DCR and PFS. **Results:** From Jul 2019 to Jan 2022, 23 pts were eligible and enrolled. Baseline characteristics: median age 69 yrs; primary: mucosal 60.9%, cutaneous 13.0%, unknown primary 13.0%, acral 13.0%; gene mutation status: Braf 17.4%, Nras 4.3%; 69.6% got extra-hepatic metastasis: regional or distant lymph node 56.3%, lung 37.5%, bone 31.3%; LDH > ULN 26.1%; median size of injected lesions: 35mm(10-94mm); median number of liver metastasis: 7(1-10); median number of injection: 10 (3-36). Among these pts, 20 pts could be evaluated for efficacy. The median PFS was 7.0 months (95%CI: 4.3-9.7 months) and the median OS was 18.6 months (95%CI: 13.4-23.7 months) with a median follow-up time of 19.8 months (range, 0.9-29.7). The global ORR by investigator was 15% (3/20), DCR 50% (10/20); the response rate was 35%(7/20) for injected lesions, 27.8%(5/18) for non-injected lesions in liver, and 26.7% (4/15) for extra-hepatic metastases. Biopsies of 15 pts for injected lesions at 8 to 12 weeks after first injection were examined to determine the situation of TIL infiltration. Among them, the median PFS of the pts (7/15) with impressive TIL infiltration (Brisk n = 4 and Nonbrisk n = 3 according to the definition of AJCC 8th edition) was 7.8 months (95%CI: 2.8-12.8 months) versus 4.1 months (95%CI: 0-9.1 months) of the pts without impressive TIL infiltration. For pts (21.7%(2 PR and 3 SD)) with no melanoma cells residual by immunohistochemistry in biopsies the median PFS was 13.8 months (95%CI: 4.0-23.6 months), and it was much longer than that of other pts which was 5.6 months (95%CI: 2.4-8.8 months). The median OS of the pts with no melanoma cells was 19.7 months (95%CI: 7.5-31.9 months). **Conclusions:** Systemic toripalimab combined with intrahepatic OrienX010 injection has shown remarkable long PFS and OS in melanoma pts with liver metastases. Clinical trial information: NCT04206358. Research Sponsor: None.

9552 **Poster Session**

IMPemBra, a phase 2 study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in patients with melanoma harboring the BRAFV600 mutation: Three-year survival data and translational analyses.

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Background: Continuous combination of MAPK pathway inhibition (MAPKi) and anti-PD-(L)1 showed high response rates, but also high frequency of treatment-related adverse events (TRAE) in BRAFV600-mutated melanoma patients (pts). Short-time MAPKi already induces T cell infiltration in pts and was synergistic with anti-PD-1 in a pre-clinical model. This phase 2b trial aimed to identify the optimal duration of MAPKi with dabrafenib + trametinib (D+T) in combination with pembrolizumab (PEM). We have previously shown that no SUSARs were observed, toxicity was related to duration of D+T, and response rates increased after addition of D+T. Here we present 3-year PFS and OS data and results of translational analyses. **Methods:** In IMPemBra, pts with treatment-naïve BRAFV600E/K mutant advanced melanoma started with PEM 200mg Q3W. After 2 cycles, pts were randomized to continue PEM only (cohort 1) or to receive in addition intermittent dabrafenib 150 mg BID + trametinib 2mg QD for 2 x 1 week (cohort 2), 2 x 2 weeks (cohort 3) or continuous for 6 weeks (cohort 4). All cohorts continued PEM for up to 2 years. Primary endpoints were safety, treatment adherence and immune-activating capacity of the different regimens. Secondary endpoints were objective response rate (ORR) and PFS, OS was an exploratory endpoint. For survival analyses, pts that received D+T (cohort 2-4) were pooled. **Results:** Thirty-two pts were randomized, 56% were male, 53% had M1c disease and 88% had a LDH level < ULN. No new grade 3-4 TRAE were observed; frequencies were 12%, 12%, 50% and 62% for pts in cohort 1, 2, 3 and 4, respectively. ORRs were 75% in cohort 1 and 2, and 88% in cohort 3 and 4. The frequency of $PD1^{+}CD8^{+}$ T cells in peripheral blood decreased slightly during treatment and there were no differences between cohorts. In cohort 1 and 2, an increase in IFNγ signature in tumor biopsies was already observed after 6 weeks of PEM, in cohort 3-4 an increase in IFNγ signature was observed in week 9, after addition of D+T. The same pattern was observed for $CD8^{+}$ T cell infiltration and PD-L1 expression. After a median follow-up of 43.5 months, the median PFS of pts treated with PEM monotherapy was 10.6 months versus 32.3 months for pts treated with PEM plus D+T ($p = 0.19$). The 3-year PFS rates were 25.0% and 50.0% respectively. Median OS was 40.5 months in the PEM pts and not reached for pts treated with PEM plus D+T ($p = 0.32$); 3-year OS rates were 62.5% and 70.8% respectively. **Conclusions:** IMPemBra demonstrated that short-term addition of intermittent D+T to PEM seems a more feasible, tolerable and an effective alternative for the continuous triple combination. In addition, it gives the opportunity to treat with second line targeted therapy after disease progression. Therefore, this regimen should be considered for further investigation in a larger cohort. Clinical trial information: NCT02625337. Research Sponsor: MSD.

9553 **Poster Session**

Updated results from the skin cancer cohorts from an ongoing phase 1/2 multicohort study of RP1, an enhanced potency oncolytic HSV, combined with nivolumab (IGNYTE).

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Background: RP1 is an enhanced potency oncolytic version of HSV1 that expresses human GM-CSF and the fusogenic protein GALV-GP R-. IGNYTE is a multicohort phase 1/2 study that evaluates the safety and efficacy of RP1 in combination with nivo (NCT03767348) in a range of tumor types. Preliminary data demonstrated a durable anti-tumor activity and tolerability for RP1+nivo. Here, we present updated results from the initial and melanoma (mel) and anti-PD1 naïve non-melanoma skin cancer (NMSC) cohorts with RP1+nivo. **Methods:** RP1 is administered via intratumoral injection Q2W, up to 10 mL/visit, first alone at a dose of 10^6 PFU/mL and then starting with the 2^{nd} dose at 10^7 PFU/mL in combination with nivo (240 mg IV Q2W for 4 months (mos) then 480 mg IV Q4W up to 2 yrs) for up to 8 doses, with the option to re-initiate RP-1. Eligible patients (pts) must have at least one measurable & injectable tumor of ≥ 1 cm, ECOG 0-1, and no prior oncolytic therapy. For mel, both anti-PD1 naïve and failed pts were eligible, for NMSC pts who were anti-PD1 naïve. **Results:** As of data extraction on January 31, 2022, 13/36 pts with mel (36.1%) and 19/31 pts with NMSC (61.3%) had a best response of PR or CR. For mel this was 5/8 (62.5%), 6/16 (37.5%), 0/6 and 2/6 (33.3%) for pts with anti-PD1 naïve cutaneous, anti-PD1/anti-PD1+anti-CTLA-4 failed cutaneous, uveal and mucosal mel respectively. For the anti-PD1 naïve NMSC this included 11/17 (64.7%), 1/4 (25%), 3/4 (75%) and 4/6 (66.6%) patients with CSCC, BCC, MCC and angiosarcoma respectively, including 8/17 (47.1%) being CR for CSCC. Current immature median DOR was 13.27 mos (current range 3.67-16.93 mos) for mel, and 7.32 mos (current range 1.88-23.11mos) for anti-PD1 naïve NMSC. Any grade TEAE (> 25%) in all cohorts combined were fatigue, nausea, pyrexia, chills, diarrhoea, pruritus, and influenza-like illness. TEAE ≥grade 3 (> 5%) were disease progression and fatigue. No deaths related to RP1 was observed, with one death related to nivo (myocarditis). Biomarker data from paired biopsies indicated robust T cell infiltration and an increase in tumor inflammation gene signature post-treatment. Clinical responses observed were independent of baseline tumor PD-L1 expression status. **Conclusions:** RP1 in combination with nivo provides a durable anti-tumor activity in pts with skin cancers, including anti-PD1 failed and anti-PD1/anti-CTLA-4 failed mel. The combination continued to be generally well tolerated with no new safety signals identified. Based on this data, enrollment into both a registration-directed cohort of pts who have anti-PD1 failed cutaneous mel (n = 125) and a cohort of pts with anti-PD1 failed NMSC (n = 30) is ongoing. Up-to-date data from this ongoing trial will be reported at the conference. A randomized Ph2 trial of RP1+cemiplimab vs. cemiplimab alone in anti-PD1 naïve NMSC is also underway (NCT04050436). Clinical trial information: NCT03767348. Research Sponsor: Replimune Group Inc.

9554 **Poster Session**

A phase II study to evaluate the safety and efficacy of IMM-101 in combination with checkpoint inhibitors in patients with advanced melanoma: Final results of the IMM-101-015 trial.

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Background: IMM-101 is a suspension of heat-killed whole cell *Mycobacterium obuense* (NCTC 13365), which enhances the innate immune response and dendritic cell maturation. In animal models, it increases antigen specific responses and number of CD8+ CTL and CD4 + Th1 cells. The clinical studies with IMM-101 have shown promising efficacy signals in pancreatic cancer when combined with gemcitabine and in melanoma as adjunctive or single agent. **Methods:** IMM-101-015 is an open-label Phase 2a study to investigate the safety and efficacy of IMM-101 in combination with checkpoint inhibitors (CPIs) in patients (pts) with advanced melanoma who were either treatment-naive (cohort A), or whose disease had progressed during PD-1 blockade (cohort B). Pts with evaluable lesions, adequate performance status and organ function were eligible. Pts received 1.0 mg of IMM-101 every 2 weeks for the first 3 doses followed by a rest period of 4 weeks, then every 2 weeks for the next 3 doses, and thereafter every 4 weeks. Nivolumab was given every 2 or 4 weeks (dependent on Investigator choice). Pts in cohort B had the option to change to ipilimumab and IMM-101 if their disease continued to progress. Biopsies and blood samples were obtained at baseline and during treatment for assessment of tumor biomarkers and immune correlatives. The primary objectives of the study were to evaluate the overall response rate (ORR) after a maximum of 18 months of treatment by RECIST 1.1 and to assess the safety and tolerability of the combination of IMM-101 + CPIs. **Results:** Sixteen pts (11 Cohort A and 5 Cohort B) were treated between October 2018 and May 2021. The median age was 68.5 yrs (range 36-92) and 11 (69%) were male. The ECOG ps was 0 in 9 (56%) and 1 in 7 (44%) pts. Four (25%) had unresectable stage III melanoma and 12 (75%) stage IV. In Cohort A (3 stage III, 5 stage IV M1b and 3 M1c) 3 pts (27%) had an elevated baseline LDH, 6 (55%) a positive PD-L1 status and 3 (27%) a BRAF mutation. Pts in cohort A were on study for a median time of 8.5 months (range 1.5 - 19.1) and those in cohort B for 3.0 months (range 1.5 - 7.4). All pts were evaluated for response. The ORR was 73% (95% CI 39.03, 93.98) in cohort A whereas all pts in cohort B reported progressive disease. With respect to cohort A, 2 (18%) pts had CR, 6 (55%) PR and 1 (9%) SD. The median progression-free survival time was 10.2 months (95% CI 2.50, NE) with 41% of the pts progression-free at 18 months. The most frequent treatment emergent adverse events (TEAEs) were injection site reaction (63%), pruritus (44%), fatigue (38%), skin rash (25%), hypothyroidism (25%) and diarrhoea (19%). There were no grade 4 TEAEs. Grade 3 TEAEs occured in 10 patients (63%), mostly skin toxicity (19%) and lab abnormalities (13%). **Conclusions:** IMM-101 in combination with nivolumab is safe and shows encouraging antitumor activity in treatment-naive patients with advanced melanoma. Clinical trial information: NCT03711188. Research Sponsor: Immodulon Therapeutics Ltd.

9555 **Poster Session**

Clinical predictors of longer survival in patients with BRAF^{V600}-mutated metastatic melanoma receiving immunotherapy prior to BRAF/MEK inhibition in the metastatic setting.

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Background: Patients with advanced BRAF^{V600}-mutated melanoma are typically treated with immunotherapy in the first-line setting, followed by BRAF/MEKi upon disease progression based on an absolute 20% improvement in 2-year overall survival over initial treatment with BRAF/MEKi in the DREAMseq trial. Our goal was to identify clinical predictors of longer survival for patients treated in our institution with this approach. **Methods:** We identified 40 patients with BRAF^{V600}-mutated metastatic melanoma treated at our institution from 2011 to 2020 with immunotherapy followed by BRAF/MEKi upon progression. Clinical data were collected and analyzed by Cox regression and Kaplan-Meier methods. Favorable outcome was defined as survival > 2 years (y) after starting BRAF/MEKis. **Results:** Median follow up was 33 months (m, 3 – 172 m). Median age was 54 y (20 - 83). Most patients were female (n = 24, %). Most patients were initially treated with ipilimumab plus nivolumab (n = 34, 85%), with 13 of these patients (38%) tolerating all 4 cycles of initial ipilimumab. Adverse events of any grade were seen in 28 (70%) patients after first-line immunotherapy, with the most common being hepatitis, colitis, hypothyroidism, rash, and fatigue. Median duration of first-line immunotherapy was 3.5 m (.75 - 42.5 m). Most common sites of progression on immunotherapy were lymph nodes (n = 14, 35%), liver (n = 12, 30%), bone (n = 10, 25%) and brain (n = 10, 25%). Prior to BRAF/MEKis, median ECOG-PS was 1 (0-4) and median LDH was 268 mg/dL (151 - 11,300). Most common BRAF/MEKi regimen was dabrafenib plus trametinib (n = 34, 85%). Adverse events of any grade were seen in 30 (75%) patients, with the most common being fever, fatigue, nausea, and vomiting. Best response to BRAF/MEKi was CR (n = 4, 10%), PR (n = 26, 65%), SD (n = 4, 10%) and PD (n = 6, 15%), and at the data cutoff, 35 (87.5%) patients progressed on BRAF/MEKi. Median duration of BRAF/MEK inhibition was 7 m (0.5 – 106 m). Median survival since starting BRAF/MEKi was 19.2 m (1.7 – 106 m). On multivariable analyses assessing predictors of survival, presence of bone metastases after disease progression on first-line immunotherapy was associated with worse 2-year survival after initiation of BRAF/MEKi (OR 2.5, 95% CI, 0.51-5.6, p = 0.0121). Other factors, such as ECOG-PS 0-2, normal LDH prior to BRAF/MEKi, and age at metastatic diagnosis < 60 years were not significantly associated with longer survival after initiation of BRAF/MEKi. **Conclusions:** We showed that the presence of bone metastases upon progression on first-line immunotherapy was associated with worse 2-y survival on salvage BRAF/MEKi for patients with BRAF^{V600}-mutated metastatic melanoma. Predictive and prognostic biomarkers for long-term response to both immunotherapy and BRAF/MEKi are needed to optimize treatment strategies and patient outcomes. Research Sponsor: None.

9556 **Poster Session**

Efficacy and tolerance of systemic therapies in metastatic melanoma of unknown primary versus known cutaneous: A multicenter retrospective study from the MelBase French Cohort.

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Background: Melanoma of unknown primary (MUP) account for 3% of all melanomas. Clinical outcome of advanced MUP in the era of novel therapies including immunotherapies (ICI) and targeted therapies (TT) have been only scarcely studied, whereas a possibly different biologic background might introduce changes in its management. Recent retrospective studies suggested that patients with advanced MUP could benefit at least as much from novel therapies as patients with known primary cutaneous melanoma (cMKP). **Methods:** Based on the nationwide MelBase prospective database (NCT02828202) this retrospective study included patients with advanced melanoma treated with first-line ICI, TT or CT. MUP was defined by upfront occurrence of (sub)cutaneous, nodal and/or visceral metastasis without any known prior or concomitant primary tumor. Patients with primary mucosal or ocular melanoma were excluded. Both progression-free survival (PFS) and overall survival (OS) were analyzed as co-primary variables in MUP vs cMKP, stratified by treatment subset (ICI vs TT vs CT vs whole cohort). Secondary variable was treatment-related toxicity. Multivariate analyses and propensity score analysis were performed. Objective: To investigate the efficacy and safety of systemic treatments (ICI, TT and chemotherapy (CT)) in patients with advanced MUP comparatively to stage-matched cMKP. **Results:** A total of 1882 patients were analyzed, including 265 (14.1%) MUP. Most patients were treated with first-line ICI. Median follow-up was 16 months. Patients in the MUP cohort more often displayed unfavorable initial prognostic factors (Table). PFS and OS did not significantly differ in MUP compared to MKP patients (p=0.73 and p=0.93 respectively). Stratification of cohorts by treatment type and application of propensity score did not lead to data modification. Treatment-related toxicity rate and severity did not differ between MUP and MKP, regardless of treatment type. **Conclusions:** Our results suggest that advanced MUP should be managed with similar strategies as advanced MKP. In our cohort, MUP patients benefited from novel therapies as much as MKP patients despite less favorable baseline prognostic factors. Exploratory studies investigating mutational burden and host immunity are needed to identify the underlying mechanisms. Research Sponsor: None.

Baseline characteristics	MKPN=1617	MUP N=265	p-value
Age, years (median (range))			
Sex, N (%)	66 (21-97)	64 (18-92)	1.0
Men	965 (60)	164 (62)	0.54
AJCC 7th edition, N (%)			
III	247 (15)	8 (3)	**<0.001**
IV	1370 (85)	257 (97)	
Brain metastases, N (%)			
Yes	289 (18)	100 (38)	**<0.001**
ECOG PS, N (%)			
0	1189 (74)	178 (67)	0.27
1	309 (19)	61 (23)	
≥2	119 (7)	26 (10)	
Mutation Status, N (%)			
BRAF V600	653 (40)	97 (37)	0.24
LDH, N (%) > ULN			
N > ULN	467 (29)	85 (32)	0.32
N > 2 x ULN	125 (8)	33 (12)	**0.01**
First line treatment			
ICI	1059 (66)	165 (62)	0.44
TT	488 (30)	86 (33)	
CT	70 (4)	14 (5)	

9557 **Poster Session**

Prophylactic lymphaticovenous bypass performed during complete lymphadenectomy is oncologically safe.

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Background: Lymphaticovenous anastomosis (LVA) is a physiologic surgery indicated for secondary lymphedema of the extremities, particularly for disease refractory to conservative management. Immediate lymphatic reconstruction (ILR) is prophylactic LVA concurrently performed with CLND. After the transected lymphatics are mapped through a dye injection, they are anastomosed to a nearby venous outflow tract. Though prophylactic LVA is increasingly being performed, its risk on cancer recurrence and distant metastasis is currently unknown. The purpose of this study was to compare the distant-metastasis free survival (DMFS) and relapse-free survival (RFS) times in melanoma patients who underwent prophylactic LVA during CLND versus those who underwent conventional CLND for grossly metastatic disease. Our study is the first prospective evaluation of the impact of prophylactic LVA on DMFS in patients undergoing CLND. **Methods:** This was a prospective study of patients with cutaneous melanoma who underwent CLND with concurrent LVA (LVA group) or CLND alone (comparison group) between 2012 and 2021. Patients were excluded if they had non-melanoma skin cancers, stage IV cancers before CLND, microscopic lymphatic disease only or follow-up time of less than 12 months who did not die from melanoma-related causes. The comparison group consisted of all consecutive patients that underwent CLND alone and met inclusion criteria. To reduce surgical technique variability, all cases were performed by a single, high-volume surgeon at a tertiary care center. **Results:** A total of 46 melanoma patients underwent prophylactic LVA during this time period. Twenty-three of these patients met all inclusion criteria and were included in the LVA group. Twenty-two consecutive patients that underwent CLND alone were included in the comparison group. All patients underwent either axillary or inguinal CLND. Average number of lymph nodes removed during CLND were 18.20 ± 9.61 and 17.04 ± 9.97 for the LVA and comparison groups, respectively ($p = 0.69$). Size of largest metastatic tumor in lymph nodes was 45.91 ± 35.03 mm and 44.54 ± 23.32 mm, respectively ($p = 0.99$). Average time to first recurrence diagnoses was 6.75 ± 3.54 months vs 8.28 ± 5.66 months. For distant metastases only, the average time to first recurrence diagnoses was 6.16 ± 3.79 months and 9.39 ± 6.19 months, respectively ($p = 0.25$). There was no significant difference in recurrence type between the two groups ($p = 0.66$). There were no differences in DMFS and RFS times between the LVA and comparison groups. **Conclusions:** Prophylactic LVA performed for grossly metastatic melanoma does not negatively impact DMFS nor RFS. Considering the extremely aggressive nature of melanoma, our finding is potentially applicable to other cancers that are amenable to CLND and LVA. Research Sponsor: None.

9558 **Poster Session**

Preferences for adjuvant immunotherapy in patients with resected stage III melanoma: A discrete choice experiment.

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Background: Adjuvant immunotherapy has revolutionized the management of resectable melanoma, substantially reducing the risk of recurrence but at the risk of immune-related adverse events (AE). This study aimed to quantify patients' preferences for adjuvant immunotherapy, the influence of varying levels of key attributes, and baseline characteristics associated with preferences. **Methods:** We performed a discrete choice experiment (DCE), including patients with resected stage III melanoma considering or having received adjuvant immunotherapy. Patients chose between twelve randomly presented choice tasks of two alternative options (adjuvant immunotherapy versus observation without adjuvant immunotherapy). The two options varied across two-three levels of six attributes: chance of 3-year melanoma recurrence, mild, permanent, or fatal AE, drug regimen, and out-of-pocket costs. We calculated the marginal rate of substitution (MRS, how much an individual was willing to trade one attribute for preferred levels of another) and willingness-to-pay (WTP, maximum price to trade their preferred attributes) per year. **Results:** One hundred and sixteen patients completed the DCE. Patients chose adjuvant immunotherapy over observation without adjuvant immunotherapy in 70% of choice tasks. Patients preferred adjuvant immunotherapy with reduced probabilities of recurrence (OR 0.76, 95% CI 0.70-0.83, p<0.001), fatal AE (OR 0.60, 95% CI 0.44-0.80, p=0.006), permanent AE (OR 0.94, 95% CI 0.89-0.99, p=0.046), and lowered out-of-pocket costs, for those with lower incomes (OR 0.63, 95% CI 0.47-0.85, p=0.003) and higher incomes (OR 0.84, 95% CI 0.15-4.86, p=0.064). Patients accepted an increase in their chance of mild AE from 1% to 37% (OR 2.06, 95% CI 1.13-3.78, p=0.019) in return for adjuvant immunotherapy. Willingness-to-pay was lower for patients with incomes that were lower rather than higher: US$595 (95% CI US-$555 to 1,305) and US$1,638 (95% CI US$ -1,235 to 3,419) per year for adjuvant immunotherapy with an absolute reduction of 1% in the 3-year risk of recurrence. **Conclusions:** Almost three-quarters of patients preferred adjuvant immunotherapy over observation without adjuvant immunotherapy. Patients were more likely to select immunotherapy if the risk of melanoma recurrence and the chance of fatal AE were reduced. Understanding patient preferences and acceptable trade-offs for adjuvant immunotherapy may allow better-informed decisions for individuals and assist policymakers in decisions about access and subsidization of effective and expensive treatments. Research Sponsor: Australian National Health and Medical Research Council (NHMRC), Cancer Institute New South Wales, Melanoma Institute Australia, Sydney Catalyst, Nicholas and Helen Moore, and the University of Sydney.

9559 **Poster Session**

Early quality of life (QOL) and symptom analysis from the DREAMseq phase III randomized control trial of combination immunotherapy versus targeted therapy in patients (pts) with *BRAF*-mutant metastatic melanoma (MM) (ECOG-ACRIN EA6134).

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Background: Combinations of either immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) or BRAF/MEK-targeted therapies have shown significant clinical benefit in pts with BRAFV600 mutant MM. Until recently, little prospective data existed to guide the choice of initial therapy or sequence. Results of the DREAMseq Trial showed that the treatment sequence beginning with nivolumab/ipilimumab (Nivo/Ipi) immunotherapy produced a clinically meaningful 20% improvement in 2-year overall survival (OS) compared to the sequence beginning with dabrafenib/trametinib (Dab/Tram) targeted therapy. The OS and progression-free survival (PFS) curves were biphasic crossing at 10 and 6 months, respectively. Our aim is to characterize QOL trends within and between the initial therapies through 24 weeks (wks). **Methods:** 265 pts were randomly assigned to Nivo/Ipi for up to 12 wks then Nivo alone (Arm A) or Dab/Tram continuously (Arm B) and at disease progression (PD) received the alternate therapy. QOL was assessed by the PROMIS Profile 29 at baseline, wk 12 (end of cycle (C) 2), and wk 24 (end of C4). Wilcoxon Signed Rank test was used to examine changes over time within treatment arms. OS was estimated by Kaplan-Meier method to compare between pts who stopped treatment for toxicity on Arm A by C2 and who continued on Arm A therapy to C4. A complete case analysis compared QOL domain means for (C2) vs. (C4). Pt-reported adverse events were also collected. **Results:** Baseline completion rates for the PROMIS-29 for Arm A (n = 108, 81.2%) and Arm B (n = 117, 88.6%) and decreased to 28.6% and 53.8%, respectively at C4. Through C4, the principal reasons for dropout were toxicity (35.2% for Arm A and 11.9% for Arm B) and PD (26.1% for Arm A and 18.6% for Arm B). From Baseline to C2: Arm B reported statistically significant improvements in Pain Interference (-3.45, P = 0.007), Sleep (-2.11, P = 0.014), and Anxiety (-3.74, P < 0.001). By C4, these early differences had dissipated (mean diff. = 0.73 – 1.73, all p = NS). For pts remaining on treatment to C4 (n = 157), a complete case analysis indicates no significant QOL differences between C2 vs C4. Pts stopping for toxicity on Arm A after C2 had similar 2-yr OS to pts who continued on Arm A to C4. QOL at C2 (Arm A: stopping for toxicity vs. on treatment) were meaningful, but underpowered (Physical Health (PH) mean difference = -3.5, p = 0.18). **Conclusions:** Over the first 12 wks, Dab/Tram is associated with significant improvement in overall function and less disturbance in in sleep, pain, physical function, and PH than Nivo/Ipi as expected by PFS curves and toxicity profiles. These differences dissipate by 24 wks when Arm A therapy has switched to Nivo alone and PFS curves cross. Early QOL and treatment cessation due to Nivo/Ipi toxicity was not associated with differences in 2-yr OS. Clinical trial information: NCT02224781. Research Sponsor: U.S. National Institutes of Health.

9560 **Poster Session**

Safety and efficacy of combined melphalan percutaneous hepatic perfusion (M-PHP) and ipilimumab plus nivolumab (IPI+NIVO) in metastasized uveal melanoma (mUM): First results of the phase Ib part of the CHOPIN trial.

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Background: Uveal melanoma (UM) is the most frequent intraocular malignant tumor in adults. Approximately 50% of all patients (pts) will develop metastatic disease in the liver. Until now, there is no systemic therapy that has been shown to improve overall survival (OS), apart from tebentafusp. M-PHP is frequently applied for liver-only UM. However, the majority of pts eventually develops extrahepatic disease after M-PHP. IPI+NIVO has been shown to induce up to 20% response rates in mUM. Our observations that checkpoint inhibition was most effective on extrahepatic UM disease has led to the CHOPIN trial testing the combination of M-PHP and IPI+NIVO. Here we present the safety and efficacy data of the phase 1b part of CHOPIN. **Methods:** Adult pts with confirmed measurable hepatic mUM and WHO PS 0-1 were included. Two courses of 6 weekly M-PHPs (melphalan 3mg/kg, max 220mg) were combined with four courses IPI+NIVO three-weekly escalating the dosing from 1mg/kg each IPI+-NIVO (cohort 1) to IPI 1mg/kg + NIVO 3mg/kg (cohort 2). Primary endpoint was safety of IPI+NIVO plus M-PHP. Secondary endpoints were best overall response (BOR) according to RECIST 1.1, progression-free survival (PFS), and OS. **Results:** 7 pts were included (4 male, median age 63.6 years (range 50-74)). Both cohorts were tolerated with no dose-limiting toxicities or deaths. Grade III/IV adverse events (AE) were observed in 2/3 pts in cohort 1 and in 3/4 pts in cohort 2 consisting of SIRS, febrile neutropenia, cholecystitis, neutropenia, thrombopenia, leukopenia, increased transaminases and fever. Grade I/II immune-related AEs occurred in all pts (myositis, hypothyroidism, hepatitis and dermatitis). BOR was 1 complete response, 5 partial responses and 1 stable disease accounting for an objective response rate (ORR) of 85.7%. At a median FU time of 20.2 months, 4 pts have an ongoing response. Currently the median PFS is 22.4 months, and all pts are still alive. **Conclusions:** Combining M-PHP with IPI+NIVO is safe at a dosing of IPI 1 mg/kg and NIVO 3 mg/kg and very promising ORR, PFS and OS have been observed. The randomized phase II part comparing M-PHP versus M-PHP+I-PI+NIVO is currently recruiting. Clinical trial information: NCT04283890. Research Sponsor: Bristol Myers Squibb and Delcath Systems Inc.

9561 **Poster Session**

A phase 1b/2a study of safety and efficacy of NT-I7 in combination with anti-PD-L1 (atezolizumab) in patients with anti-PD-1/PD-L1 naïve or relapsed/refractory (R/R) high-risk skin cancers: The phase 1b report.

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Background: Novel immunotherapy approaches have changed the treatment landscape of patients (pts) with high-risk cancers like melanoma, Merkel cell carcinoma (MCC) and cutaneous squamous cell carcinoma (cSCC). However, despite the widespread use of checkpoint inhibitors (CPI) in these indications, most pts either fail to respond or eventually have progressed. NT-I7 (efineptakin alfa) is a long-acting human IL-7 that can increase the number and functionality of T-cells in peripheral blood and within the tumors. NT-I7 in combination with atezolizumab (atezo), may augment the efficacy in high-risk skin cancers. **Methods:** This is a phase 1b/2a study to evaluate the safety and efficacy of NT-I7 in combination with atezo in pts with CPI- naïve or relapsed/refractory (R/R) high-risk skin cancers. Phase 1b dose escalation followed a 3+3 design, in which pts who received NT-I7 IM every 3 weeks (Q3W) at 3 dose levels (DL1-3): 120, 360, and 840 μg/kg or Q6W at DL4 1200 μg/kg, and atezo IV 1200 mg Q3W. The objectives of the phase 1b were to evaluate dose-limiting toxicity (DLT), determine the MTD and the recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics and preliminary antitumor activity. **Results:** As of January 14, 2022, 16 pts were enrolled in phase 1b: DL1 (n = 3), DL2 (n = 3), DL3 (n = 7), and DL4 (n = 3). The median age was 66 years [46-86], with ECOG PS 0 in 6 (37%), 1 in 7 (44%) and 2 in 3 (19%), and median number of prior therapies 1 [1-2]. One pt had a DLT at DL3 [Grade (G)3 confusion and G3 increased AST] but no DLTs were reported at DL4 and MTD was not reached. The RP2D was 1200 μg/kg Q6W of NT-I7 plus atezo 1200 mg Q3W. All pts had drug related AEs. Most AEs were G 1- 2 in 11(69%) pts; 5 (31%) in G3. There were no related G4/G5 AEs. Eleven pts had stable disease and the disease control rate was 69% (11/16). Preliminary PK analysis of DL1- 3 showed dose dependent C_{max}, with T_{max} at ~24hr and $T^1/_2$ ranging ~75hr to 125hr. NT-I7 dose-dependent expansion of the absolute lymphocyte count, $CD3^+$, $CD4^+$ and $CD8^+$ T-cells peaked after one dose and the increase was maintained by repeat dosing until the end of treatment. Immunophenotyping of memory T-cell subsets showed a 5-fold expansion in most T-cell subsets and a 30-fold expansion of the stem cell memory CD8+ T-cell subset (Tscm) at DL4. **Conclusions:** This trial is the first time an IL-7 cytokine-based therapy and CPI has been assessed in UV induced high-risk skin cancers including in IO refractory pts. The combination of NT-I7 and atezo showed favorable safety and anticancer activity. NT-I7 significantly increased total lymphocyte and the T-cell compartment, with a greatest expansion of the CD8+ Tscm, a vital population for eliciting antitumor activity. Additional safety and efficacy updates will be provided by the ongoing phase 2a trial in CPI-naïve cSCC and MCC and CPI R/R MCC, cSCC and melanoma. Clinical trial information: NCT03901573. Research Sponsor: Neoimmunetech, Inc.

9562 **Poster Session**

Distinct mutational landscapes characterize melanomas metastatic to different anatomical sites.

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Background: Despite revolutionary advances in systemic therapies for melanoma, many patients with metastatic disease have limited treatment options and some sites of disease remain particularly challenging to control, such as brain and liver metastases. We sought to define anatomical site-specific mutational profiles of melanoma metastases from which potentially novel personalized therapeutic opportunities may be developed. **Methods:** Targeted exome genomic profiling was performed via the FoundationOneCDx platform and known or likely pathogenic variants retained for analysis. PD-L1 immunohistochemistry was performed with the Dako 22C3 assay with PD-L1+ defined as tumor proportion score ≥1. Tumor mutational burden (TMB)-high was defined as TMB ≥10mut/Mb. UV signature was calculated using established algorithms. Aberrations in 23 genes potentially actionable in melanoma (*BARD1*, *BRAF*, *BRCA1/2*, *CDKN2A*, *DDX3X*, *FANCC*, *HRAS*, *IDH1*, *KIT*, *KRAS*, *MAP2K1*, *NF1*, *NRAS*, *PALB2*, *PIK3CA*, *PPP6C*, *PTEN*, *RAC1*, *RAD51C/D*, *RB1*, *TP53*) were compared across metastatic sites including skin, lymph node, lung, liver, and brain. **Results:** A total of 4918 cutaneous-type melanoma tumors was evaluated, including 2854 skin lesions (primary/metastasis) and metastases from lymph nodes (n = 858), liver (n = 194), lung (n = 342), and brain (n = 200). The commonly mutated genes were *CDKN2A* (2220/4918, 45.1%), *BRAF* (2148/4918, 43.7%), *NRAS*(1347/4918, 27.4%), *NF1* (1038/4918, 21.1%), *TP53* (1234/4918, 25.1%) and *PTEN* (1038/4918, 13.5%). Compared with skin lesions, metastases to the lung were enriched for variants affecting *NF1* (OR 2.57, p = 8.99e-13), *TP53* (OR 1.65, p = 3.04e-04) and depleted in *NRAS* (OR 0.49, p = 9.00e-06) and *BRAF* (OR 0.70, p = 1.13e-02). Lung metastases were associated with higher prevalence of UV signatures, PD-L1 positivity and high TMB. *PTEN* variants were enriched in both brain (OR 3.00, p = 2.38e-08) and small intestine (OR3.46, p = 6.63e-3) metastases. Brain metastases were also enriched for *CDKN2A* variants (OR 1.56, p = 4.50e-02). Lymph node metastases had lower rates of UV signatures, *NF1* variants, or high TMB, but were associated with PD-L1 positivity. Positional analysis of variants revealed that several, including *NRAS*, *MAP2K1*, *KRAS*,*HRAS*, *IDH1*, *RAC1*, *GNA11* and *GNAQ* were highly restricted to hotspot loci, without definite variation by metastatic site. Conversely, variants affecting *CDKN2A*, *PTEN*, *TP53* and *NF1* were distributed widely across the gene, with high levels of non-hotspot mutations observed in skin lesions, suggesting that such non-hotspot subclones contribute less to distant metastatic potential and are lost during disease evolution. **Conclusions:** We observed distinct and organ site-specific mutational patterns in patients with metastatic melanoma. These data raise the possibility of metastatic phenotype-directed therapy to improve the personalization and outcomes of treatment for this disease. Research Sponsor: None.

9563 **Poster Session**

Adjuvant dabrafenib plus trametinib (D + T) versus placebo in patients with resected stage III *BRAF*^{V600}-mutant melanoma: Updated 5-year distant metastases-free survival (DMFS) analysis of COMBI-AD.

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Background: DMFS is an important endpoint for patients with stage III cutaneous melanoma, as delaying or preventing systemic disease is associated with improved clinical and patient-reported outcomes. Prior results from the phase 3 COMBI-AD trial (NCT01682083) showed 5-year DMFS rates of 65% with adjuvant D + T vs 54% with placebo (PBO; hazard ratio [HR] = 0.55; 95% CI: 0.44-0.70). An analysis of DMFS by AJCC-7 stages IIIA-C suggested a similar benefit of D + T vs PBO regardless of stage (Dummer R et al. *N Engl J Med*. 2020). Here, we report 5-year DMFS rates by AJCC-8 stages IIIA-D, other prognostic subgroups, and results of a regression tree analysis with DMFS. **Methods:** Patients with resected AJCC-7 stage III *BRAF*$^{V600E/K}$-mutant melanoma were randomized to either D (150 mg twice daily) + T (2 mg once daily) or 2 matched PBOs for 12 months. Primary endpoint was relapse-free survival (RFS); DMFS was a secondary endpoint. Kaplan-Meier survival analyses were performed to assess the long-term benefits for DMFS rates with D + T vs PBO. The regression tree analysis (data cutoff: 5 years) for all patients (N = 870) evaluated potential prognostic/predictive factors of long-term DMFS including baseline age, sex, region, *BRAF* mutation type, body mass index, lactate dehydrogenase levels, ECOG, T and N categories, histology, primary tumor ulceration, treatment type, number of lymph nodes with metastases, tumor mutational burden, and interferon-gamma gene expression signature (IFN-γ GES). **Results:** At 5 years, DMFS rates were higher for patients with AJCC-8 stages IIIB-D disease receiving adjuvant D + T vs PBO (table). Five-year DMFS rates also favored D + T vs PBO in subgroups of patients with microscopic or macroscopic lymph node involvement (table) and those with or without primary tumor ulceration and/or in-transit metastases. A regression tree revealed T and N stage, treatment type, and IFN-γ GES as important variables defining 5-year DMFS subgroups. **Conclusions:** In this retrospective analysis, adjuvant D + T provided long-term DMFS benefit vs PBO in stage IIIB-D patients with resected *BRAF*$^{V600E/K}$-mutant melanoma. Key clinical and patient factors impacting DMFS were similar to prior RFS findings (ESMO 2021; Robert C et al. *Ann Oncol*. 2021) and included T and N stage, treatment type, and IFN-γ GES. These results further validate the robust long-term clinical benefit of adjuvant D + T for patients with melanoma. Clinical trial information: NCT01682083. Research Sponsor: Novartis Pharmaceuticals Corporation.

	Stage								Lymph node involvement			
	IIIA		IIIB		IIIC		IIID		Macroscopic		Microscopic	
Statistic	D + T n = 50	PBO n = 39	D + T n = 145	PBO n = 154	D + T n = 217	PBO n = 214	D + T n = 22	PBO n = 17	D + T n = 158	PBO n = 161	D + T n = 152	PBO n = 157
5-year DMFS rate, %	75.3	84.5	66.5	52.8	63.0	50.8	64.6	25.6	63.3	47.1	75.3	62.5
HR (95% CI)	1.24 (0.42-3.63)		0.56 (0.38-0.83)		0.54 (0.39-0.75)		0.20 (0.07-0.55)		0.52 (0.37-0.75)		0.49 (0.31-0.79)	
Log-rank *P*	0.695		0.004		< 0.001		0.001		< 0.001		0.002	

9564 **Poster Session**

Prognostic significance of the CP-GEP assay combining clinicopathologic factors and gene expression profiling in patients (pts) with AJCC v8 stage I/II cutaneous melanoma (CM).

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Background: AJCC v8 includes Breslow thickness and ulceration to subdivide stage I and II CM pts into risk groups. In light of the results from adjuvant therapy in stage II CM, it has been discussed that pts' follow-up and eventually treatment should consider additional markers, namely CP-GEP, to further refine the risk classification provided by the AJCC v8. The aim of this single center study was to clinically validate a prognostic CP-GEP-based risk score for stage I/II CMs combining Breslow, age and the expression of 8 genes *SERPINE2*, *GDF15*, *ITGB3*, *CXCL8*, *LOXL4, TGFBR1*, *PLAT* and *MLANA*. **Methods:** All obtainable formalin-fixed paraffin-embedded primaries of stage I/II CMs with negative sentinel lymph node (SLN) from the Central Malignant Melanoma Registry of Germany diagnosed between 2000-2017 and archived in Tuebingen were included. Study hypothesis and protocol were prospectively formulated. Tumors were analyzed blinded to clinical outcome. Quantitative reverse transcription polymerase chain reaction of the 8 genes was performed and combined with age and tumor thickness to define CP-GEP low- vs. high-score groups. Relapse-free survival (RFS), distant metastasis free survival (DMFS) and overall survival (OS) were evaluated using Kaplan-Meier curves. CP-GEP score performance was tested using multivariate Cox regression adjusted for tumor thickness, ulceration and age. **Results:** We included 543 pts with Stage IA (n=78); IB (n=223); IIA (n= 123); IIB (n=73); IIC (n=46). 43% were females, median Breslow was 1.7mm and 25% of tumors had ulceration. The median follow-up was 78 months (IQR 47-116). 311 (57%) patients had a high-risk CP-GEP score. The 5-y RFS rate was 71% and 92% (HR 4.2; p<0.001), the 5-y DMFS rate was 86% and 96% (HR 4.35; p<0.001) and the 5-y OS was 85% and 95% (HR 3.2; p=0.001), respectively for high and low-risk CP-GEP score. In multivariate Cox regression analysis for RFS including Breslow thickness, ulceration and age, contribution of CP-GEP score remained independently significant (HR 2.75; p=0.0008) compared to age (HR 1.03; p<0.0007), Breslow (HR 1.21; p<0.0001) and ulceration (HR 1.37; p=0.1694). **Conclusions:** CP-GEP risk score is a non-invasive and independent prognostic model for risk of relapse in stage I/II melanoma validated in this study. It identifies SLN negative pts at high risk of relapse and should be considered for complementing AJCC classification and for inclusion in future clinical trials. Research Sponsor: SkylineDX.

5y-RFS, DMFS and OS rates.

	CP-GEP high N=311	CP-GEP low N=232	IA N=78	IB N=223	IIA N=123	IIB N=73	IIC N=46	All N=543
5y RFS % (95% CI)	71 (65-76)	92 (87-95)	96 (85-99)	89 (83-92)	75 (65-82)	69 (57-79)	41 (25-55)	80 (76-83)
5y DMFS % (95% CI)	86 (81-90)	96 (92-98)	96 (84-99)	96 (92-98)	91 (84-96)	82 (69-90)	60 (42-74)	90 (87-93)
5y OS% (95% CI)	85 (80-89)	95 (91-97)	97 (90-99)	97 (93-98)	86 (77-91)	80 (68-88)	65 (48-78)	89 (86-92)

9565 **Poster Session**

Immune profiling of metastatic uveal melanoma and response to immune checkpoint inhibitors.

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Background: Response to immune checkpoint inhibitors (ICI) in uveal melanoma (UM) is low. We aimed to elucidate tumor markers correlated with improved survival in ICI treated UM patients. **Methods:** Tumor samples of UM patients were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes assay or whole exome sequencing) and RNA (whole transcriptome sequencing). Somatic mutations were totaled to calculate tumor mutational burden (TMB) and cutoff for high vs low was 10 mt/MB. PDL1 was tested with immunohistochemistry for tumor staining and cutoff was ≥2+, 5% for high vs low. *NCOA2* gene amplification was considered a surrogate for gain of chromosome 8q (cutoff ≥6). Median RNA expression level for LAG3 was calculated for each cohort and used as cutoff for high vs low. All ICI treated patients were considered to have metastatic disease. Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from tissue collection to last contact. Time on treatment (TOT) was calculated from start to finish of ICI treatment and was considered as surrogate for progression-free survival (PFS). Comparison of survival was performed by Kaplan-Meier analysis. **Results:** A total of 450 UM samples were analyzed. Of these, 108 were from ICI treated patients and were obtained from primary (10/108) or metastatic (98/108) sites. Most tumors were PDL1 low in the entire UM (86%, 240/279) and ICI treated (62%, 55/89) cohorts. There was no difference in TOT between PDL1 high vs low in ICI treated cohort (HR 1.46, 95% CI 0.82-2.6, median TOT 3.1 months vs 2.3 months). Similarly, 98% (257/263) of all UM samples had low TMB. ICI treated patients with high LAG3 expression had similar TOT compared to low (HR 1.3, 95% CI 0.59-2.9, median TOT 6 months vs 2 months). In the entire UM cohort, most tumors were *NF1*-wildtype (95%, 56/59). *NF1*-wildtype status was associated with a longer rwOS compared to *NF1*-mutated (HR 0.18, 95% CI 0.051-0.64, median rwOS of 20.8 months vs 7 months). *NCOA2* amplification was associated with a worse rwOS as compared to patients without *NCOA2* amplification in the entire UM (HR 0.68, 95% CI 0.50-0.91) but not in ICI treated cohort (HR 0.84, 95% CI 0.52-1.4). There was no difference in TOT in ICI treated patients by *BAP1* and *SF3B1* mutational status. **Conclusions:** UM lacks traditional markers of response to ICI. Short TOT seen in our study is consistent with PFS of 3 to 5.5 months seen in clinical trials. High LAG3 expression was associated with a clinically significant improvement in TOT. Traditional markers of poor prognosis were not implicated in survival differences in ICI treated patients. This likely represents a poor prognosis in all mUM patients regardless of traditional prognostic markers. *NF1* mutation is uncommon in UM and its significance as a prognostic marker should be validated in a larger cohort. Ongoing research is needed to understand the biology of UM and approach to treatment. Research Sponsor: None.

9566 **Poster Session**

The relationship between circulating tumor DNA with Merkel cell carcinoma tumor burden and detection of recurrence.

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Background: Merkel cell carcinoma (MCC) is an aggressive skin cancer with a recurrence rate of 40%. Early detection of recurrence can improve outcomes, and effective surveillance is crucial for management of patients with MCC. While Merkel cell polyomavirus (MCPyV) oncoprotein serology is useful in surveillance for MCPyV-positive MCC tumors, patients with MCPyV-negative tumors have no available blood biomarkers and require frequent imaging. This prospective, multicenter study assessed whether circulating tumor DNA (ctDNA) can assess disease burden and detect recurrence regardless of virus status. **Methods:** A total of 328 blood samples were collected from 125 patients at various time points with a median follow-up of 6 months (range: 0-21 months) between April 2020 to January 2022. Whole-exome sequencing was performed on tumor tissue and matched normal blood to identify a set of somatic, clonal single nucleotide variants, which were tracked in subsequent blood (plasma) samples using a personalized and multiplex PCR-NGS based ctDNA assay (Signatera). Clinically evident disease was defined as MCC noted either by physical exam or by imaging, and molecular evidence of disease was defined as a positive ctDNA test. Surveillance phase began once there was no clinically evident or molecular evidence of disease. **Results:** Among 125 patients, 47 (38%) had clinically evident MCC and all were found to be ctDNA-positive at the first time point (sensitivity: 100%; 95% CI: 91-100%). Of the 47, 24 were newly diagnosed with MCC and had a median primary tumor size of 2.2 cm (range 0.5-8.5 cm) and a median ctDNA value of 26 mean tumor molecules (MTM)/mL (range: 0.08-1470 MTM/mL). Primary tumor diameter and ctDNA value were strongly correlated (Spearman's $r = 0.81$, $p < 0.001$). Of the 125 patients, 73 (58%) patients were assessed in the surveillance setting and had a total of 152 plasma samples available for longitudinal ctDNA testing. Over this period, 7 ctDNA tests were positive while 145 were negative. After a positive test, 5/7 developed a clinically evident recurrence (4 within 60 days). Of the remaining 2 without clinical recurrence, one had < 60 days of follow-up at time of data analysis. The estimated risk of recurrence, accounting for incomplete follow-up, was 57% within 60 days of a positive ctDNA test (n = 7 tests). In contrast, after a negative ctDNA test (n = 145 tests), the risk of recurrence was 0% within 60 days and 3% between 60-90 days. **Conclusions:** To our knowledge, this is the largest study to explore ctDNA testing in MCC patients. This study demonstrates that ctDNA testing can detect MCC recurrence early and is a promising clinical surveillance tool regardless of tumor viral status. Research Sponsor: U.S. National Institutes of Health, MCC Patient Gift Fund.

9567 **Poster Session**

Plasma methylated DNA markers of cutaneous melanoma: Association with PET/CT-positive disease.

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Background: Cutaneous melanoma surveillance is important to identify low-volume systemic disease, but imaging is costly and poorly accessible to patients; frequent skin checks lack sensitivity and specificity. We aimed to establish clinical feasibility of a liquid biopsy blood test, which quantifies validated, melanoma-specific, methylated DNA markers (MDMs), previously discovered, and reported by our team, using tissue extracted DNA. **Methods:** We prospectively collected blood from adult patients with histologically confirmed melanoma metastases and no other internal malignancies (within 5-years) who underwent surveillance by FDG-PET/CT (N = 88). Blood from age- and sex balanced cancer-free controls (N = 100) were compared. From PET/CT, we extracted the number of organs involved, SUV-max, and largest tumor diameter. Unequivocal metastasis was defined as SUV ≥ 4 and largest diameter > 5 mm. Because PET/CT is inadequate for the screening of brain metastases, we excluded the brain from the analysis. MDMs (*chr11.149, HOXA9, chr20.210, FLJ22536, CLIC5, SIX4, chr7.155, chr17.730, chr1.110*) were assayed using target enrichment long-probe quantitative-amplified signal assays, normalized to *B3GALT6*, in blinded fashion. Using a logistic regression approach and nine candidate MDMs, we calculated the sensitivity for detecting patients with metastasis on PET/CT at 100% specificity. **Results:** 52/88 (59%) of melanoma patients showed evidence of metastasis on PET/CT at the time of blood draw. At 100% specificity, a panel of 4 MDMs (*HOXA9, chr20.210, chr17.730, chr1.110*) yielded a sensitivity of 86.5% (45/52 cases) vs. 100 cancer-free controls. When applying this model to the 36 PET/CT-negative patients, specificity was as high as 97.2% (35/36 cases) while maintaining a sensitivity of 86.5% (one patient with a positive test result had a complete metabolic response to binimetinib / encorafenib prior to negative PET/CT). For patients with ≥ 2 organs involved by metastasis, sensitivity was 100% (29/29 cases). False-negative cases had metastasis in single organs and were characterized by minimal tumor burden and oral corticosteroid use. One false-negative patient had localized stage III disease without known primary melanoma. **Conclusions:** Plasma MDM levels appear highly concordant with FDG-PET/CT in patients with metastatic cutaneous melanoma. A liquid biopsy approach has potential to lower cost and improve patient access to surveillance. Additional prospective studies in larger intended use cohorts are needed to validate our results. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

9568 **Poster Session**

The effect of the microbiome on immune checkpoint inhibitor toxicity in patients with melanoma.

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Background: Immune-checkpoint inhibitor (ICI) immunotherapy has increased survival in patients with melanoma. However, only half of the patients respond, and many experience immune-related adverse events (irAEs). Recent evidence suggests that modification of the gut microbiome may increase response to ICIs and decrease toxicity. Here we describe the first results of a clinical trial to determine if the microbiome can predict the response or toxicity during the first 16 weeks of ICI treatment. **Methods:** We enrolled patients aged 18 or older in a prospective observational cohort study at The Ohio State University Comprehensive Cancer Center Skin Cancer Clinic (OSUCCC-SCC) who were to receive treatment with pembrolizumab or nivolumab alone or in combination with other treatments (e.g. nivolumab and ipilimumab) for melanoma. Patients receiving systemic or oral corticosteroids at the start of ICI cycle 1 were excluded but were eligible if receiving adrenal physiologic replacement. Patients collected stool samples at baseline, within 2 days of an adverse event (if applicable), and at 12 weeks. The response to ICIs was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) at a 12-week computed tomography scan. Metagenomic whole-genome shotgun sequencing was performed on an Illumina NovaSeq 6000 and then classified using HUMAnN3. The effect of microbe relative abundances on potential irAEs was modeled by logistic regression with the R package glmm. **Results:** In total, 88 patients consented to the trial. Pre-treatment microbiome samples were collected from 49 patients. Potential irAEs were observed in 16 out of the 49 patients for whom pre-treatment microbiome samples were collected. There was no significant difference in the ages ($p = 0.150$, genders ($p = 0.2$), stages ($p = 0.2$) or treatments ($p = 0.07$) of those who developed potential irAEs. Pre-treatment abundance of the family *Ruminococcaceae* was most strongly associated with the development of a potential irAE ($p = 0.03$), followed by a taxon in an unclassified order within the phylum *Firmicutes* ($p = 0.05$). The family *Bacteroidaceae* was most strongly associated with no potential irAE ($p = 0.05$). **Conclusions:** Longitudinal and event-driven biospecimen collection in the context of treatment with immunotherapies was feasible in the OSUCCC-SCC. The abundance of the two high-taxonomic rank microbe groups was significantly associated with potential irAEs. The association with *Ruminococcaceae* is consistent with previous studies where it was associated with response to ICIs and, in separate studies, development of an irAE was associated with a better response. The unclassified taxon is potentially a new biomarker for the prediction of toxicity and a therapeutic target to reduce treatment side effects. Future analyses will associate microbes with treatment response and test for consistent microbiome changes at the time of irAE development. Clinical trial information: NCT05102773. Research Sponsor: Pelotonia Junior Investigator Award.

9569 **Poster Session**

The efficacy of immune checkpoint blockade for melanoma in-transit with or without nodal metastases: A multicenter cohort study.

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Background: Guidelines addressing melanoma in-transit metastasis (ITM) recommend immune checkpoint inhibitors (ICI) as a first-line treatment option, despite the fact that there are no efficacy data available from prospective trials for exclusively ITM disease. The aim of this study was to analyze the outcome of patients with ITM treated with ICI based on data from a large cohort of patients treated at international high-volume melanoma centers. **Methods:** A multicenter retrospective cohort study of patients treated between January 2015 and December 2020 from Australia, Europe, and USA, evaluating treatment with ICI for ITM with or without nodal involvement (AJCC8 N1c, N2c and N3c) and without distant disease (M0). Patients were treated with PD-1 inhibitor (nivolumab or pembrolizumab) and/or CTLA-4 inhibitor (ipilimumab). We assessed response rates, progression-free survival (PFS), melanoma-specific survival (MSS) and overall survival (OS). **Results:** A total of 287 patients from 21 institutions in 8 countries were included. Immunotherapy was first-line treatment in 64 (22%) patients. Monotherapy with a PD-1 or CTLA-4 inhibitor was given in 233 (81%) and 23 (8%) patients respectively, while 31 (11%) received both in combination. Overall response rate was 56%, complete response (CR) rate 36% and progressive disease (PD) rate 32%. Median PFS was 10 months (95% CI 7.4-12.6 months) with a 1-, 2- and 5-year PFS rate of 48%, 33% and 18% respectively. Median MSS was not reached, and the 1-, 2- and 5-year MSS rates were 95%, 83% and 71% respectively. **Conclusions:** Systemic immunotherapy is an effective treatment for melanoma ITM. Future studies should evaluate the optimal role for systemic immunotherapy in the context of multimodality therapy including locoregional treatments such as surgery, intralesional therapy, and regional therapies. Research Sponsor: Institutional support from Knut and Alice Wallenberg Foundation.

9570 **Poster Session**

Multicenter real-world data of adjuvant treatment and disease outcome of patients with melanoma with high-risk of recurrence.

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Background: Clinical trials demonstrated a significantly improved recurrence-free survival (RFS) of melanoma patients treated adjuvantly with immune checkpoint inhibition (ICI) and targeted therapy (TT). As data from controlled trials are based on selected populations, we investigated melanoma patients with high risk of recurrence who opted for ICI, TT, or no adjuvant treatment (NoTx) under real-world conditions. **Methods:** In a prior analysis of this multicenter, retrospective cohort study, patients with resected melanoma stage III-IV between 06/2018 and 09/2019 were analyzed for adjuvant therapy choice (Lodde et al., Cancers 2021). In this follow-up study, the treatment course of ICI- and TT-treated patients as well as recurrence characteristics, subsequent management and outcomes also including NoTx patients were examined. **Results:** 814 patients were included (72 stage IIIA, 266 IIIB, 383 IIIC, 24 IIID, 69 IV; 309 BRAF mut); 533 patients received ICI (66%), 114 TT (14%, 36.9% of all BRAF mutated patients), 167 patients had opted for NoTx (21%). Median treatment duration was 10.2 and 11.7 months for ICI and TT, respectively. ICI was discontinued prematurely in 51% (273/533) and TT in 44% (50/114) of patients. The main reason for discontinuation was progressive disease (PD) in ICI patients (58%, 158/273) and adverse events in TT patients (60%, 33/50). At a median follow-up (FU) of 24.6 months for ICI, 25.3 months for TT, and 21.8 months for NoTx, 48% of ICI (255/533), 35% of TT (40/114), and 45% of NoTx (75/167) patients had developed a recurrence mostly at distant sites (ICI 62%, TT 63%, NoTx 64%). In patients with recurrence, median time from start of adjuvant treatment to 1st recurrence was 6.1 months in ICI and 17.6 months in TT. Median RFS was 32.0 months for ICI (95% CI 25.7-38.3), not reached for TT, and 22.3 months for NoTx (95% CI 15.2-29.4). Among BRAF mut patients with stage III, risk of recurrence was higher for ICI than TT (hazard ratio adjusted for age, sex and tumor stage, 2.31; 95% CI 1.56-3.43). Subsequent systemic treatment for the 1st recurrence was given in 76% (192/253) of ICI, 83% (33/40) of TT, and 53% (40/75) of NoTx patients. Among patients who received the 1st subsequent systemic treatment for metastatic disease, PD was the best response in 67% (82/123) for ICI, 55% (11/20) for TT, and 50% (16/32) for NoTX. **Conclusions:** After 2 years of FU, recurrences were mostly at distant sites in all groups. ICI had higher discontinuation rates and more and earlier recurrences than TT. BRAF mut melanoma patients treated with ICI had a significantly higher risk of relapse than TT-treated patients. Response to subsequent systemic treatment was low for both ICI and TT. Research Sponsor: None.

9571 **Poster Session**

Use of Merlin Assay to identify patients with a low-risk for SN metastasis in a prospective multicenter Dutch study of a primary melanoma gene-signature (CP-GEP model) to predict sentinel node status during COVID-19.

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Background: Approximately 70%-85% of patients who undergo sentinel lymph node biopsy (SLNb) show no nodal metastasis in the sentinel node (SN). The clinicopathological and gene expression profile (CP-GEP) model (*Merlin Assay*) was developed and validated to identify patients that may forgo the SLNb surgery due to their low risk for for nodal metastasis This study was initiated during the first wave of Covid-19 pandemic to allow for surgical triage on SLNb and evaluate the implementation of the Merlin assay in clinical practice. **Methods:** This study was conducted in four designated melanoma centers in the Netherlands. Patients (age > 18y) with newly diagnosed melanoma of the skin, eligible to undergo SLNb were screened for study inclusion. Main exclusion criteria was prior history of primary melanoma (> T1b) in the past 5 years. After enrollment, tissue sections of the primary melanoma were centrally reviewed at the Erasmus MC Cancer Institute to determine Breslow thickness at primary diagnosis. FFPE tumor tissue was dispatched for molecular analysis of eight target genes known to play a role in cancer development. In combination with age, Breslow thickness, and GEP outcome, risk of having nodal metastasis was calculated. Results were binary presented as 'CP-GEP low risk' and 'CP-GEP high risk'. SLNb status was used as gold standard for comparison. **Results:** A total of 177 patients were analyzed using the CP-GEP model. Median age was 64 years (IQR 52-73) Median Breslow thickness was 1.4mm (IQR 1.0-2.4). Of all patients 28.2% was diagnosed with T1, 40.7% with T2 and 20.9% with T3 melanoma. Corresponding positivity rate was 7%, 14% and 29% respectively. A total of 24 out of 177 patients had a positive SLNb. Median turn-around time from inclusion to CP-GEP result was 15 days. Overall 37.1.% of patients had a CP-GEP low risk profile. The CP-GEP model had a NPV of 94.6%. **Conclusions:** This is the first prospective multicenter implementation study for the Merlin assay. Results are in line with previous validation studies. The CP-GEP model could accurately identify patients at low risk for SN metastasis. Implementation in clinical practice is feasible based on current turn-around time. In the future, using the Merlin assay to deselect patients for SLNB may allow for a reduction of surgery in patients with melanoma. Research Sponsor: None.

9572 **Poster Session**

Survival update of neoadjuvant ipilimumab + nivolumab in macroscopic stage III melanoma: The OpACIN and OpACIN-neo trials.

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Background: OpACIN was the first trial testing neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) versus the same combination given adjuvant. An unexpected high pathologic responses of 78% was observed in the neoadjuvant arm with a 2-year relapse-free survival (RFS) rate of 80%. The subsequent OpACIN-neo trial tested 3 different dosing schedules of neoadjuvant IPI + NIVO and identified 2 cycles IPI 1 mg/kg + NIVO 3 mg/kg q3w as most favorable schedule with a pathologic response rate of 77% and 20% grade 3-4 immune-related adverse events. Long-term data on the durability of the pathologic (path) responses upon neoadjuvant checkpoint inhibition are lacking so far. Therefore, we present here the updated RFS and overall survival (OS) data of both trials. **Methods:** In OpACIN 20 macroscopic stage III melanoma pts were randomized to receive either IPI 3 mg/kg + NIVO 1 mg/kg q3w 4 cycles adjuvant after lymph node dissection or split 2 cycles neoadjuvant and 2 adjuvant. In OpACIN-neo 86 macroscopic stage III melanoma pts were randomized to arm A (2x IPI 3 mg/kg + NIVO 1 mg/kg q3w, n=30), arm B (2x IPI 1 mg/kg + NIVO 3 mg/kg q3w, n=30), or arm C (2x IPI 3 mg/kg q3w followed by 2x NIVO 3 mg/kg q2w, n=26) followed by lymph node dissection in week 6. RFS and OS were estimated using Kaplan Meier method. All comparative efficacy endpoints are descriptive for OpACIN, since the trial was not powered for comparison of the arms. **Results:** After a median follow-up (FU) of 68.6 months for OpACIN (minimum FU of 59.8 months), median RFS and OS were not reached. Only 1/7 patients (pts) with a pathologic response on neoadjuvant therapy has relapsed. Estimated 5-year RFS and OS rates for the neoadjuvant arm were 70.0% (95%CI: 46.7-100.0) and 90.0% (95%CI: 73.2-100.0) versus 60.0% (95%CI 36.2-99.5) and 70.0% (95%CI: 46.7-100.0) for the adjuvant arm. After a median FU of 46.8 months for OpACIN-neo (minimum FU of 38.2 months), median RFS and OS were not reached. Of pts with path response on neoadjuvant therapy, 3/64 (4.7%) had an event (2 pts relapsed, 1 pt died due to toxicity), versus 14/21 (66.7%) without path response. This resulted in a 3-year RFS rate of 95.3% (95%CI: 90.3-100.0) for responding versus 36.8% (95%CI: 20.4-66.4) for non-responding pts ($p<0.001$). Of the pts who relapsed after response, 1 had major path response (<10% vital tumor) and 1 a partial response (10-15% vital tumor). Estimated 3-year RFS and OS rates are presented in the Table. **Conclusions:** Updated data from OpACIN and OpaCIN-neo trials confirm the durability of responses upon neoadjuvant combination checkpoint inhibition in high risk stage III melanoma. Pathologic response remains a reliable surrogate marker for RFS and OS. Clinical trial information: NCT02437279, NCT02977052. Research Sponsor: BMS, with NKI as sponsor.

	3-year RFS (95%CI)	3-year OS (95%CI)
OpACIN	80.0% (58.7-100.0)	90.0% (73.2-100.0)
OpACIN-neo	81.9% (74.1-90.6)	91.9% (86.3-97.8)
Arm A	86.7% (75.3-99.7)	90.0% (79.9-100.0)
Arm B	79.3% (65.9-95.5)	93.3% (84.8-100.0)
Arm C	79.2% (64.5-97.2)	92.3% (82.6-100.0)

9573 **Poster Session**

SALVO: Single-arm trial of ipilimumab and nivolumab as adjuvant therapy for resected mucosal melanoma.

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Background: Mucosal melanoma is a rare, highly aggressive form of melanoma with extremely high recurrence rates, despite definitive surgical resection. Median RFS has been reported to be 5.4m, with RFS rates at 1 and 2 years of 10%, and 0%, respectively (Lian B, Si L, Cui C, et al. Phase II Randomized Trial Comparing High-Dose IFN-α2b with Temozolomide Plus Cisplatin as Systemic Adjuvant Therapy for Resected Mucosal Melanoma. *Clinical Cancer Research* 2013, **19**(16):4488-4498). Currently there is no consensus on recommendations for adjuvant therapy. Data on the use of immune checkpoint inhibitors (ICI) adjuvantly is lacking. **Methods:** We performed a single arm, multicenter clinical trial using "flip dose" ipilimumab (1mg/kg q3w x4 cycles),and nivolumab (3 mg.kg q3w x4 cycles), then Nivolumab 480 mg q4w x 11 cycles to complete a year of adjuvant therapy. The primary endpoint was recurrence-free survival (RFS), and the study had 85% power to detect an improvement in RFS between 5.5 and 9.5 months using a one-sided log rank test. Participants must have had R0/R1 resection <90 days prior to registration, and no prior systemic therapy (adjuvant radiation allowed), ECOG 0/1, no uncontrolled significant autoimmune disease or other invasive cancer. Patients were recruited through the Midwest Melanoma Partnership/Hoosier Oncology Network. **Results:** From 9/17 to 8/21, 44 patients were approached at 6 centers. Of these 9 were ineligible, and 35 were enrolled. Of these, 29 (83%) had R0 resections, and 7 (20%) had adjuvant radiation prior to enrollment. As of Dec 2021, 31 patients have completed the treatment phase. Of the 35 patients treated on study, 20 patients have recurred (7 local, 5 distant, 3 regional, 5 sites unconfirmed), 6 stopped therapy due to adverse effects, and 8 have died. The mean age of patients was 65.8 years and 21 (60.0%) were female. The primary site of disease was vulvovaginal N=12 (32.4%) patients, sinonasal N= 11 (29.7%), anorectal N= 9 (24.3%) and other site N= 5 (13.5%). Adjuvant radiation had been given in 7 pts. Driver mutations were rare, with only 3 (8.6%) patients having a KIT mutation, and one patient (2.9%) each having a NRAS or BRAF mutation. RFS rates at 1 and 2 years were 50% (95% CI 31-66%) and 37% (95% CI 19-55%), with OS rates at 1 and 2 years of 87% (95% CI 68-95%) and 68% (95% CI 46-83%). Median RFS was 10.3 m (95% CI5.7-25.8). Most common grade 3 adverse events were diarrhea (14%), hypertension (14%), hyponatremia (11%), with no grade 4/5 toxicities. **Conclusions:** Flip dose ipilimumab and nivolumab after resection is associated with outcomes improved over previously reported outcomes in the absence of therapy. Long term follow up is ongoing as are subgroup analyses and correlative studies. Clinical trial information: NCT03241186. Research Sponsor: Bristol Myers Squibb.

9574 **Poster Session**

Primary ipilimumab/nivolumab followed by adjuvant nivolumab in patients with locally advanced or oligometastatic melanoma: Update on outcome.

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Background: The aim of neo-adjuvant therapy in locally advanced or oligometastatic melanoma is to facilitate radical resection, improve outcomes and undertake research to identify biomarkers of response and resistance. The optimal schedule to balance efficacy vs toxicity in dual PD1/CTLA4 blockade regimens remains a matter of debate. We initiated an open- label, single arm study to investigate the Nivo 3/ Ipi 1 schedule as primary treatment of locally advanced or oligometastatic melanoma patients (pts). **Methods:** Treatment schedule consists in 4 neoadjuvant cycles of Ipilimumab 1 mg/kg and Nivolumab 3 mg/kg every 3 weeks, followed by surgery and adjuvant Nivolumab 480 mg every 4 weeks for 6 cycles. Primary objective is pathological complete remission (pCR) rate, according to Neoadjuvant Melanoma Consortium criteria. Secondary objectives are: safety, feasibility and efficacy; QoL; identification of molecular and immunological biomarkers of response and resistance (somatic genetic drivers, tumor mutational burden, mutational signatures, predicted neoantigens, germline HLA typing, somatic HLA mutations and liquid biopsy); degree of immune activation; evaluation of microbioma. **Results:** From March 2019 to April 2021, 35 pts were included within the trial. All pts completed the treatment program. 6 pts (17%) developed immune-related (IR) G3-4 adverse events (AE): 3 transaminitis, 1 pneumonitis, 1 myocarditis and 1 CPK increase; all of them but one underwent surgery after toxicity resolution. 4 pts (11%) experienced G3-4 non-IR AE. 31 pts underwent surgery after neoadjuvant phase: pCR, near pCR, pathological partial remission (pPR) and pathological no response (pNR) were achieved in 18 (58%), 2 (7%), 4 (13%) and 7 (22%) cases, respectively. 2 pts progressed before surgery and 8 pts progressed during/after adjuvant phase (6/8 in NR at surgery). 4 pts died, 3 after disease progression and 1 for ischemic stroke 5 months after the end of therapy. At 18 months, progression free survival (PFS) and overall survival (OS) were 80 and 85%, respectively (median follow-up: 23 months); non responders (pNR) have a higher risk of relapse or death vs responders (pCR+near pCR+pPR) [HR= 4.11, 95%CI (0.96 -17) adjusted for age, p=0.06]. **Conclusions:** Our study lends further support to the adoption of the Nivo 3/ Ipi 1 schedule as primary treatment for locally advanced/oligometastatic melanoma, as this regimen achieved a pCR/near pCR rate of 65% with a rate of severe IR-AEs (17%) lower than previously reported in CheckMate 511 trial (34%) using Nivo3/ Ipi1 schedule. Available translational data on potential genomic biomarkers of response, gut microbiome and systemic inflammatory landscape evaluated longitudinally during therapy on each patient will be presented. Clinical trial information: 2018-002172-40. Research Sponsor: BMS.

9575 **Poster Session**

Efficacy and safety of "second adjuvant" therapy with BRAF/MEK inhibitors after resection of recurrent melanoma following adjuvant PD-1–based immunotherapy.

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Background: Both anti-PD-1 antibodies and BRAK/MEK inhibitors (BRAF/MEKi) reduce the risk of recurrence for patients with resected stage III melanoma. For patients with V600 BRAF-mutated melanoma who recur with resectable disease on or after adjuvant, many may be suitable for 'second adjuvant' treatment after surgery. We sought to examine the efficacy and safety of 'second adjuvant' BRAF/MEKi in patients who recurred despite adjuvant PD-1 based immunotherapy. **Methods:** Patients with V600 BRAF-mutated melanoma treated with adjuvant PD-1 based immunotherapy for resected stage III/IV disease who recurred, underwent resection of recurrence and were then treated with adjuvant BRAF/MEKi were identified retrospectively from 13 centres. Demographics, disease characteristics, treatment details, and outcome data were examined. **Results:** 55 patients were included; median age at commencement of PD-1 was 53y, most were V600E (91%) and had IIIB (42%) or IIIC (44%) melanoma. PD-1 based adjuvant therapy included nivolumab (71%), nivolumab plus ipilimumab (14%), pembrolizumab (13%) and pembrolizumab plus mRNA-4157 vaccine (2%). Patients had initial recurrence after mean 8.4 months (95% CI 7.4-10.6), mainly while on treatment (65%), in regional nodes (42%), in-transit metastases (ITMs; 38%), both regional nodes and ITMs (7%) and distant metastases (13%). Surgical management included CLND (36%), selected nodal resection (11%), ITM resection (33%) and resection of distant metastasis (13%). A minority had adjuvant radiotherapy (17%). Stage at start of second adjuvant BRAF/MEKi included IIIB (29%), IIIC (53%) IIID (4%) and IV (15%). Patients received dabrafenib and trametinib (95%, N = 52) and encorafenib and binimetinib (5%, N = 3). After a median follow up of 21.4 months (19.7-25.4), 17 (31%) patients have recurred again. Mean duration of treatment was 9 months (95% CI 7.4-10.6); 20% ceased for toxicity, 7% for recurrence and 35% were on treatment at last follow up. The most common toxicity was pyrexia (43%) and 21% patients experienced a severe (G3-4) adverse event. Median RFS was 33.4 months (14.3.7-NR) and median DMFS was not reached. At 12 months, 72% (59-88) of patients were recurrence free and 90% (81-100) were free of distant recurrence. For those whose disease recurred again, most recurred after cessation of second adjuvant BRAF/MEKi (13/17, 76%). 7 (41%) recurred locally and 8 (47%) recurred with new metastatic disease but none had brain metastases. **Conclusions:** This is the first study examining outcomes of patients receiving second adjuvant targeted therapy for melanoma, after failure of adjuvant PD-1 based immunotherapy. While RFS appears shorter compared to first line trials, second adjuvant treatment with BRAF/MEKi appears safe and active in preventing further recurrence. Further data on sequencing adjuvant therapies are needed. Research Sponsor: None.

9576 **Poster Session**

A single-center experience of 98 patients (pts) with regionally metastatic Merkel cell carcinoma (MCC) of known (MCCKP) and unknown (MCCUP) primary at presentation.

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Background: MCC is a rare skin cancer historically associated with poor survival rates and which is increasing in incidence. A small number of retrospective series suggest that MCCUP may be associated with better prognosis than MCCKP while others report worse outcomes. Recent advances in immunotherapy have changed the multimodal treatment landscape and outcomes of advanced MCC pts. We describe our experience with the management and outcomes of pts presenting with regional MCC metastasis of known and unknown primary origin. **Methods:** A retrospective review of pts with clinical regional disease at MCC diagnosis treated at our institution from 3/2003-3/2021 was performed. Clinicopathologic variables and outcomes were assessed. Overall survival (OS), recurrence-free survival (RFS) and progression-free survival (PFS) were estimated by the Kaplan Meier method. **Results:** Of 98 pts with regional disease on exam at presentation, 56 (57%) had MCCUP and 42 (43%) had MCCKP. Median follow-up from diagnosis to last follow-up or death was 33 months. Pts were generally older (MCCUP vs MCCKP: 68.7 vs 73.1 years), male (MCCUP vs MCCKP: 82% vs 74%) and Caucasian (MCCUP vs MCCKP: 84% vs 83%). Over half the pts had a history of another malignancy (MCCUP vs MCCKP: 52% vs 60%) with 9% and 14% being immunocompromised at diagnosis, respectively. After completion of staging workup, MCCUP pts had earlier stage disease at presentation compared with MCCKP pts (stage IIIA: 80% vs 55%, IIIB: 5% vs 31%, IV: 15% vs 14%, respectively). The cervical nodal basin was most commonly involved in MCCUP pts while regional disease was more varied in MCCKP pts (MCCUP vs MCCKP: cervical 54% vs 28%, axillary 15% vs 33%, inguinal 33% vs 3%, inguinal and pelvic 0% vs 11%, in transit 0% vs 14%). Formal lymphadenectomy (LND) was performed in 27 (48%) and 18 (43%) of MCCUP and MCCKP pts, respectively. Of these pts, 33% and 50% received neoadjuvant systemic therapy, most commonly immunotherapy; 70% and 55% received adjuvant radiotherapy. MCCUP pts had better outcomes compared to MCCKP pts (Table), with longer RFS in pts who underwent LND (not reached [NR] vs 13.1 months) as well as longer PFS in pts who did not undergo LND (17 vs 9 months) with longer OS in both subgroups (LND: NR vs 102.7 months; no LND: 74.4 vs 48.7 months). **Conclusions:** MCCUP patients with regional disease on exam at presentation have improved survival compared to MCCKP. Current stage III survival estimates may underestimate survival in patients with resectable disease. Research Sponsor: None.

Last known status of MCCUP and MCCKP patients presenting with regional disease on exam.

All pts	MCCUP (n=56)	MCCKP (n=42)
Alive, no evidence of disease (NED)	28 (50%)	12 (28.6%)
Alive with disease (AWD)	11 (19.6%)	10 (23.8%)
Deceased	17 (30.4%)	20 (47.6%)
Pts who underwent LND	**MCCUP (n=27)**	**MCCKP (n=18)**
NED	19 (70.4%)	4 (23.5%)
AWD	4 (14.8%)	5 (29.4%)
Deceased	4 (14.8%)	8 (47.1%)

9577 **Poster Session**

Adjuvant treatment of in-transit melanoma: Addressing the knowledge gap left by clinical trials.

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Background: Few clinical trials address the efficacy of adjuvant systemic treatment in patients with ITM. This study describes the efficacy of adjuvant systemic therapy of ITM patients beyond the clinical trial setting. **Methods:** All stage III adjuvant-treated melanoma patients registered in the nationwide Dutch Melanoma Treatment Registry between 01-07-2018 and 31-12-2020 were included. Patients were divided into three groups: patients with ITM only, with ITM and nodal disease, and patients with nodal disease only. Differences in recurrence patterns were analysed. An exploratory analysis was performed for stage III patients who underwent surgical resection without adjuvant treatment. Recurrence-free survival (RFS) and overall survival (OS) at 12-months were assessed. **Results:** A total of 1037 stage III melanoma patients received adjuvant anti-PD-1 therapy, and 260 underwent surgical resection only. Of the adjuvant-treated patients, 16.9% had ITM only, 15.5% had ITM with nodal disease, and 66.8% had nodal disease only. Of the surgical resection only patients 20.4% had ITM only, 12.3% had ITM with nodal disease and 67.3% had nodal disease only. In the adjuvant-treated patients, 12-months RFS was comparable between patients with ITM only and patients with nodal disease only (71.1% vs. 72.2% respectively, $p = 0.95$), but significantly lower for patients with ITM and nodal disease (57.1%; ITM with nodal disease vs. ITM-only $p = 0.01$, and ITM with nodal disease vs. nodal disease only $p < 0.01$). Locoregional metastases occurred as first recurrence site in 72.7% of ITM-only patients, 42.9% of ITM and nodal disease patients and 38.9% of patients with nodal disease only, while distant recurrences occurred in 18.2% of patients with ITM only, in 36.7% of patients with ITM and nodal disease, and in 42.3% of patients with nodal disease only ($p = 0.01$). OS at 12-months was significantly higher for ITM-only patients compared to patients with ITM and nodal disease (97.7% vs. 90.6%, $p < 0.01$), and was better compared to patients with nodal disease only (97.7% vs. 94.4%, $p = 0.05$). OS at 12-months was comparable for patients with ITM and nodal disease and patients with nodal disease only ($p = 0.19$). In general, surgery-only ITM patients were older and had a worse performance score. 12-months RFS appeared worse compared to adjuvant-treated ITM patients (36.6% vs. 68.3%). In this group of surgery-only ITM patients OS at 12-months also appeared worse compared to adjuvant-treated ITM patients (89.7% vs. 95.5%). **Conclusions:** RFS rates in ITM-only patients are similar to non-ITM patients, while RFS in patients with ITM and nodal disease is shorter. Adjuvant-treated patients with ITM without nodal disease less often experience distant recurrences and have a superior OS compared to other adjuvant stage III patients. Our results suggest that other treatment strategies for ITM patients with nodal disease should be considered. Research Sponsor: None.

9578 **Poster Session**

Adjuvant temozolomide plus cisplatin versus high-dose interferon alpha-2b in resected mucosal melanoma: A randomized, multicenter, controlled, phase III trial.

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Background: Mucosal melanoma (MuM) is a rare cancer with an extremely poor prognosis and no established standard adjuvant therapy. A phase II trial showed promising outcomes with adjuvant temozolomide plus cisplatin (Chemo) versus high-dose interferon alpha-2b (HDI) in resected mucosal melanoma. We conducted the phase III trial to definitively compare these two treatments. **Methods:** In this multicenter, randomized, controlled, phase III trial, patients with pathologically confirmed stage I-III mucosal melanoma who had undergone complete resection were stratified by primary site (head and neck vs. non-head and neck) and disease stage (I/II vs. III) and randomized 1:1 to receive Chemo (temozolomide 200 mg/m^2/day orally on days 1 to 5 plus cisplatin 75 mg/m^2 i.v. on days 1-3, repeated every 3 weeks for six cycles) or HDI (15×10^6 U/m^2/day i.v on days 1 to 5 each week for 4 weeks followed by 9×10^6 U three times per week for 48 weeks). Postoperative radiotherapy was recommended for head and neck MuM patients, with a total dose of 65-70 Gy/30-35 fx to GTV and 60 Gy/30 Fx to CTV. The primary endpoint was relapse-free survival (RFS). Secondary endpoints included distant metastasis-free survival (DMFS), overall survival (OS), and safety. The protocol was registered at ClinicalTrials.gov (NCT03435302). **Results:** Between Feb 2014 and Jun 2016, 204 patients were randomized to treatment (Chemo group: n = 103, HDI group: n = 101). Baseline characteristics were generally well balanced between the two groups. Anatomic site of head and neck, gastrointestinal, gynecological were 38.8% vs 49.5%, 35.9% vs 22.8%, 25.2% vs 27.7% in Chemo and HDI group, respectively. Stage of I/II, III were 68.9% vs 73.3%, 31.1% vs 26.7% in Chemo and HDI group, respectively. CKIT, BRAF, NRAS Mutation were 7.0% vs 8.2%, 5.0% vs 8.2%, 13.4% vs 15.8% in Chemo and HDI group, respectively. In the ITT population, At a median follow-up of 64.8 months, patients receiving Chemo had a higher median RFS (15.5 vs. 9.9 months; HR = 0.622; 95% CI, 0.463 to 0.836; P = 0.001), DMFS (19.5 vs. 12.7 months; HR = 0.705; 95% CI, 0.518 to 0.959; P = 0.025) and OS (38.2 vs. 33.5 months; HR = 0.832; 95% CI, 0.598 to 1.155; P = 0.270) versus the HDI group. A subgroup analysis revealed consistent improvements in RFS, DMFS and OS with Chemo versus HDI across multiple subgroups. Toxicities were generally mild to moderate in both groups. The most common adverse events were fatigue, anorexia, nausea/vomiting, leukopenia, Neutropenia, hepatotoxicity, fever and anemia, 23 patients (22.3%) in Chemo group and 57 patients (56.4%) in HDI group had a grade 3 or 4 adverse events. **Conclusions:** Adjuvant temozolomide plus cisplatin led to a significantly lower risk of relapse and distant metastasis in patients with resected mucosal melanoma versus high-dose IFN-a2b and was generally well tolerated. Clinical trial information: NCT03435302.
Research Sponsor: National Natural Science Foundation of China, Beijing Municipal Administration of Hospitals' Youth Programme.

9579 **Poster Session**

Leveraging personalized circulating tumor DNA (ctDNA) for detection and monitoring of molecular residual disease in high-risk melanoma.

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Background: High-risk melanoma has variable prognosis. Adjuvant immuno- (IO) and targeted therapy (TT) are approved for stage III-IV resected disease. However, a significant proportion of patients (pts) are cured by local treatment alone or relapse despite adjuvant therapy. Liquid biopsy with ctDNA assays have been used to predict response to treatment and identify pts at higher risk of progression/death. Personalized ctDNA assays are a highly sensitive approach that may enhance upfront risk stratification and early detection of relapse. **Methods:** Serial ctDNA Monitoring as a predictive Biomarker in advanced neoplAsms (SAMBA) is a Princess Margaret prospective ctDNA kinetics study (NCT03702309) in high-risk melanoma pts. Plasma is collected pre-op (pre-local treatment, if feasible), post-op (after surgery), and every 3-6 months (m) until radiological progressive disease (rPD). Personalized amplicon based NGS assays by Inivata (RaDaR) were used to detect somatic variants in ctDNA identified through whole-exome sequencing of matched tumor tissue. Progression free survival (PFS) and overall survival (OS) from the time of surgery were estimated with the Kaplan Meier and compared with the log-rank test. **Results:** As of December 2021, 82 of 100 planned pts have been enrolled. A total of 191 samples from 47 pts have been analyzed. Median age was 66 years (27-87), 33 were male (70%). Seven (15%), 30 (64%) and 10 (21%) were stage II/III/IV respectively. All pts had surgery and 8 (17%) adjuvant radiation. No systemic therapy was given to 11 pts (23%); 30 (64%) had IO and 6 (13%) TT. rPD occurred in 13 pts (28%). Median follow up was 24 months. A median of 48 variants were included in the personalized ctDNA panel design (35-52). ctDNA was detected (ctDNA+) at any time point in 12/47 pts (26%), of which 5/12 (42%) were *BRAF* and *NRAS* wt on tissue. Median PFS was 4.9 months (m) for ctDNA+ pts and not reached (NR) for ctDNA- pts at post-op (HR = 2.71 CI 0.60-12.31, p = 0.179). Median OS was 23.1 m vs NR in ctDNA+ vs ctDNA- pts (HR = 8.9, CI 1.45-54.77, p = 0.004). Two ctDNA+ pts had neoadjuvant IO and became ctDNA- before surgery. One, free of disease after 12 m, had ctDNA- in 4 follow up samples. The other pt was ctDNA+ in the post-op sample and relapsed within 3 m. Four of 45 (9%) pts had ctDNA+ at post-op. Two of them, including a pt who had neoadjuvant IO, did not receive adjuvant therapy and had rPD within 3 m. The other 2 pts received adjuvant IO; ctDNA cleared and pts remain free of disease at 12 and 34 m. Three pts with rising ctDNA over time experienced rPD after a median of 4 m (2-7). **Conclusions:** Personalized ctDNA analysis with RaDaR may improve risk of death stratification and selection of pts who could benefit from adjuvant treatment. Detection of ctDNA may precede rPD. Follow-up will continue in pts with rising ctDNA who have not yet had rPD. Pts accrual and sample collection are ongoing, and additional data will be presented. Clinical trial information: NCT03702309. Research Sponsor: Princess Margaret Cancer Center institutional founding, Princess Margaret Cancer Foundation.

9580 **Poster Session**

Neoadjuvant dabrafenib and trametinib (D+T) for stage III melanoma: Long-term results from the NeoCombi trial.

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Background: Neoadjuvant D+T has a high pathologic response rate and impressive short-term survival. The NeoCombi trial (NCT01972347) enrolled 35 patients with resectable stage III melanoma, with last patient commencing treatment April 19th 2017. We report 5-year outcomes from this trial. **Methods:** Pts received 12 wks neoadjuvant standard dose D+T, then 40 wks adjuvant D+T. Eligible pts were $\geq$ 18 yrs, ECOG PS $\leq$ 1 with clinical stage III BRAF V600E/K melanoma. CT and PET scans were performed at baseline and prior to surgery. Pathologic response was determined as per International Neoadjuvant Melanoma Consortium (INMC) criteria and defined as complete (pCR), near complete, partial (pPR) or no response (pNR). CT monitoring was continued 12 wkly thereafter to 2 yrs, then 6 monthly to 3 yrs, then as standard care. The primary endpoints were the complete pathological response (pCR) and RECIST response rate (rRR) at wk 12. Secondary endpoints included relapse free survival (RFS), OS, and toxicity. **Results:** 35 pts were enrolled, 6 with IIIB, 29 IIIC (7 ITM only) disease (clinical AJCCv7). At data cut August 17th 2021, median F/U was 60 mo (95% CI 56-72). No patients progressed in the neoadjuvant phase, and (49%) had a pCR, 1 near pCR, 6 pPR, 11 pNR. 5-year RFS, DMFS and OS data are shown in the Table. The majority of recurrences occurred within the first 2 years, with no recurrences beyond 3y. 21 patients recurred; 12 (57%) had first recurrence locoregional (6/12 subsequent distant recurrence) and 9 (43%) had first recurrence in distant sites (3/9 in brain). Locoregional recurrence was managed with surgery alone in 4/12, systemic therapy alone in 2/12, or both surgery and systemic therapy in 5/12 (4/5 had adjuvant systemic therapy), 1 pt was observed until distant recurrence. Subsequent systemic therapy in the 15 patients with a distant recurrence included PD-1 based immunotherapy (N=14) and BRAF targeted therapy (N=10). **Conclusions:** Neoadjuvant D+T in clinical stage III melanoma has impressive early activity, however patients remain at high risk of recurrence. Pathologic response can identify patients at the highest risk of recurrence, offering a chance of alternative adjuvant therapy in non-responders. Clinical trial information: NCT01972347. Research Sponsor: GlaxoSmithKline, Novartis, National Health and Medical Research Council, Australia; and Melanoma Institute Australia.

	5y RFS	5y DMFS	5y OS
All (N=35)	40%	57%	80%
pCR (N=17)	53%	59%	88%
Non-pCR (N=18)	28%	55%	71%

9581 **Poster Session**

Health-related quality of life (HRQoL) with pembrolizumab (pembro) in resected high-risk stage II melanoma in the phase 3 KEYNOTE-716 study.

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Background: Adjuvant pembro improved RFS vs placebo (HR, 0.61; 95% CI, 0.45-0.82) and had manageable safety in patients (pts) with resected high-risk stage II melanoma at second interim analysis of KEYNOTE-716 (NCT03553836). HRQoL results are presented. **Methods:** Pts aged ≥12 y with resected stage IIB/C melanoma were randomized 1:1 to adjuvant pembro 200 mg (2 mg/kg for pts ≥12 and < 18 y) Q3W or placebo for ≤17 cycles. Change from baseline in HRQoL was an exploratory end point. EORTC QLQ-C30 and EQ-5D-5L were administered at baseline; cycles 5, 9, 13, and 17 in y 1; every 12 wk in y 2; and every 6 mo in y 3. The HRQoL population included all pts who received ≥1 dose of study treatment and had ≥1 HRQoL assessment available. Least-squares mean (LSM) change from baseline to wk 48 in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL) and physical functioning (PF) and EQ-5D-5L visual analog scale (VAS) were calculated using a constrained longitudinal data analysis model; HRQoL score was the response variable with treatment by time interaction and T stage at baseline as covariates. Empirical mean change from baseline in QLQ-C30 GHS/QoL and PF scores over time was evaluated. A ≥10-point improvement or decline in QLQ-C30 scores was considered clinically meaningful. Data cutoff was June 21, 2021. **Results:** Of 976 pts enrolled, 969 were included in the HRQoL population (483 pembro; 486 placebo). Median follow-up in the ITT population was 20.5 mo (range, 4.6-32.7). At wk 48, compliance (adherence) for EORTC QLQ-C30 was 83.4% for pembro and 89.3% for placebo and completion was 70.6% and 75.7%, respectively. At wk 48, compliance for EQ-5D-5L was 84.1% for pembro and 90.0% for placebo and completion was 71.2% and 76.3%, respectively. QLQ-C30 GHS/QoL and PF and EQ-5D-5L VAS scores were similar between arms at baseline. LSM change from baseline to wk 48 in QLQ-C30 GHS/QoL score was –4.49 (95% CI, –6.19 to –2.79) for pembro and –0.82 (95% CI, –2.47 to 0.83) for placebo (LSM difference: –3.67; 95% CI, –5.91 to –1.44). LSM change from baseline to wk 48 in QLQ-C30 PF score was –3.27 (95% CI, –4.61 to –1.92) for pembro and –1.77 (95% CI, –3.07 to –0.46) for placebo (LSM difference: –1.50; 95% CI, –3.33 to 0.32). LSM change from baseline to wk 48 in EQ-5D-5L VAS score was –2.19 (95% CI, –3.52 to –0.85) for pembro and –0.25 (95% CI, –1.54 to 1.04) for placebo (LSM difference: –1.94; 95% CI, –3.72 to –0.16). LSM change from baseline to wk 48 in other QLQ-C30 functioning and symptom scales was similar in both arms. Empirical mean change from baseline in QLQ-C30 GHS/QoL and PF was similar over 96 wk in both arms. **Conclusions:** No clinically meaningful decreases in EORTC QLQ-C30 or EQ-5D-5L VAS scores were observed for adjuvant pembro or placebo. These results, along with improved RFS and manageable safety, support the use of adjuvant pembro in resected high-risk stage II melanoma. Clinical trial information: NCT03553836. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

9582 **Poster Session**

Successful management of Australian patients with extensive skin field cancerization (ESFC) with widefield volumetric arc radiation therapy (VMAT): Report with 12-month follow-up.

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Background: Non-melanomatous skin cancer (NMSC) diagnoses are associated with a high risk of developing new skin cancers in adjacent areas. Patients with extensive skin field cancerization (ESFC) have large areas (generally $\geq 50 cm^2$) of compromised skin characterized by pre-cancerous actinic keratoses often requiring repeated interventions. Lesion-directed therapies have excellent cure rates, but therapies targeting a wider region have limited durability, including topical agents such as 5-flurouracil. The development of volumetric modulated arc radiation therapy (VMAT) to precisely target large, curved skin surfaces has generated interest in its application to ESFC. This is a report on the efficacy, safety, and cosmetic outcomes of VMAT in the management of patients with ESFC at facilities across five Australian states. **Methods:** Sixty-three ESFC zones on 60 patients were prescribed widefield VMAT and prospectively enrolled in the National (Australian) Dermatology Radiation Oncology Registry (NDROR). Over 80% of patients had received up to 4 prior non-radiotherapy interventions. Fields included lower and upper limb, face, scalp, or trunk regions. Total widefield VMAT RT doses ranged from 45-50 Gy delivered in 25-30 daily fractions across 5-7 weeks. 3-, 6-, and 12-month follow-up assessments rated the percentage of disease clearance, cosmesis using the Lovett's scale, and toxicity based on CTCAE. **Results:** At 12-month follow-up, 97% of treated zones had achieved and maintained clinical success, defined as > 90% field clearance. Five percent of patients exhibited recurrence of original disease, whereas 10% of patients developed a new actinic keratosis or NMSC. Cosmesis was rated as excellent or good in 98% of patients. Most patients exhibited grade 1-2 radiation-induced dermatitis during therapy, which resolved by 3-month follow-up. Grade 3 dermatitis at end of treatment was exhibited in 7% of the patients, which also resolved. Eight percent of patients discontinued treatment due to acute toxicities. The most common persistent toxicity at 12-month follow-up was localized grade 1 xerosis (dryness) at 43% and/or alopecia at 33%. **Conclusions:** Widefield VMAT achieved very promising clinical success in patients with ESFC for whom other therapies had failed. VMAT yielded favorable cosmetic outcomes, and treatment-related toxicity was manageable and transient in most patients. While additional follow up is necessary, these results demonstrate that widefield VMAT may be an excellent option for some patients with increasingly unmanageable presentations of ESFC. Research Sponsor: GenesisCare.

9583 **Poster Session**

Sentinel lymph node biopsy in Merkel cell carcinoma: A multi-institutional study from the Pan-Canadian Merkel Cell Collaborative.

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Background: There is controversy regarding sentinel lymph node biopsy (SLNB) in clinically node-negative Merkel Cell Carcinoma (MCC). We compared MCC recurrence and survival between patients who did versus did not undergo a SLNB. **Methods:** Patients with MCC across 13 Canadian centers were reviewed, from 2000-2018. Of a total cohort of 750 patients, 485 had clinically node-negative disease at presentation. A propensity score was created. The association between SLNB and local, regional and distant recurrence, and cancer-specific and overall survival were evaluated using competing risks and Cox proportional hazards regression. **Results:** 195 patients (40.2%) underwent a SLNB. SLNB was performed more commonly in younger, healthier patients with MCC located in the extremities or torso (Table). The results of 177 SLNBs were available; 60 (33.9%) were positive. SLNB-positive patients underwent completion dissection (n=15, 25%), completion dissection and nodal radiation (n=22, 36.7%), nodal radiation alone (n=18, 30%) or observation (n=5, 8.3%). Patients who did not undergo a SLNB underwent nodal radiation alone (n=40, 13.8%) or observation (n=250, 86.2%). The median follow-up was 2.7 years (range 0.2-14.4). The regional recurrence rate was 14.5% (n=17) among SLNB-negative versus 15% (n=9) among SLNB-positive patients. Among patients who did not undergo a SLNB, the regional recurrence rate was 25.2% (n=63) among those who underwent observation and 15% (n=6) among those who received nodal radiation alone. After propensity score matching, SLNB patients had a lower risk of regional recurrence (sHR 0.54 95% CI 0.34-0.86 p=0.01) and improved overall survival (HR 0.32 95% CI 0.23-0.45 p<0.01), but there was no difference in local recurrence (sHR 0.92 95% CI 0.50-1.69 p=0.79), distant recurrence (sHR 0.88 95% CI 0.52-1.49 p=0.63), or cancer-specific survival (HR 0.67 95% CI 0.31-1.45 p=0.31). **Conclusions:** SLNB is associated with a reduced risk of regional recurrence and improved overall survival. The role of SLNB in selecting patients for emerging therapies, such as immunotherapy, needs to be evaluated. Research Sponsor: None.

Clinicopathologic and treatment factors by SLNB.

	SLNB N (%)	No SLNB N (%)	P-value
Male	122 (62.6)	166 (57.2)	0.24
Age (mean +/- sd)	70 +/-10	79 +/- 10	<0.01
Charlson Co-Morbidity Index [3] 4	108 (55.4)	228 (78.6)	<0.01
Primary Location			<0.01
Head & Neck	52 (26.7)	178 (61.4)	
Extremities	130 (66.7)	92 (31.7)	
Torso	13 (6.7)	6.9 (20)	
Stage			<0.01
I	84 (43.1)	183 (63.1)	
II	45 (23.1)	100 (34.5)	
III	66 (33.8)	7 (2.4)	

9584 **Poster Session**

Analysis of the effect of systemic corticosteroids on survival from tebentafusp in a phase 3 trial of metastatic uveal melanoma.

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Background: All immune therapies that rapidly activate T cells, including T cell engagers, can induce cytokine release syndrome (CRS). Tebentafusp (tebe), a T cell receptor bispecific (gp100 x CD3) can also induce skin adverse events (AEs), due to gp100+ cutaneous melanocytes. CRS and skin AEs may require management with short term corticosteroids, which may also be used as premedication for subsequent tebe doses. Here we report the first analysis of systemic corticosteroid use and correlation with efficacy from a Phase (Ph) 3 trial for any T cell engager. **Methods:** Post hoc analyses were performed on the tebe arm of the Ph3 [NCT03070392] study in previously untreated HLA-A*02:01+ metastatic uveal melanoma (mUM) (N = 245). Due to the low rate of severe AEs in Ph1 trials, prophylactic corticosteroids were not mandated. The association between overall survival (OS) and corticosteroid use (new start within 30 days of first tebe dose) was investigated using landmark analyses in the safety population. Multivariate analyses were adjusted for key patient characteristics and AEs of special interest: CRS, rash, and liver function test (LFT) elevation. Steroid type (hydrocortisone vs. others) and treatment duration (1 vs. > 1 day) were also investigated. **Results:** In the Ph3 trial, 64/245 (26%) patients received new systemic corticosteroid within 30 days after the first dose of tebe, mostly for treatment of AEs (56/64, 88%) or pre-medication due to previous AE (14/64, 22%). 25 of the 64 patients received corticosteroids only for a single day. The most frequent AEs (≥15%) were rash (18/64, 28%), CRS (15/64, 23%), and hypotension (12/64, 19%). In a logistic regression model, elevated baseline LDH, the dominant prognostic marker, was most strongly associated with use of corticosteroids ($p = 0.01$). In the multivariate analysis, corticosteroids were not associated with any significant OS difference (HR 1.41, 95% CI 0.83-2.4, $p = 0.2$) and this effect did not differ in patients with or without CRS, rash or LFT elevation (all interaction tests $p > 0.2$). There was no difference in OS according to corticosteroid type or whether administered for 1 vs > 1 day. **Conclusions:** This is the first analysis from a phase 3 trial of the impact of systemic corticosteroids on survival for a T cell engaging cancer therapy. The vast majority of tebe-treated patients (84%) either did not require corticosteroids (74%) or only received them on a single day (10%). The most frequent reason for corticosteroid use was an emergent AE, including CRS and rash. Corticosteroid use following the pre-specified AE guidelines was not associated with any significant impact on OS. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9585 **Poster Session**

Treatment with tebentafusp beyond radiographic progressive disease (PD) in metastatic uveal melanoma (mUM).

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Background: Tebentafusp (tebe) is the first T cell receptor therapeutic to demonstrate overall survival (OS) benefit in a randomized Phase 3 study vs investigator's choice (IC) [NCT03070392]. OS benefit was also observed in patients (pts) with best objective response (BOR) PD (HR 0.43), and in pts who had tumor growth ≥20% as best change in tumor size (HR 0.41), suggesting tebe-treated pts may exhibit atypical radiological responses and could benefit from treatment beyond radiographic progression (TBP), a well-established concept in immuno-oncology. Here we analyzed tumor kinetics and clinical benefit in pts treated with tebe beyond initial radiographic progression (TBP). **Methods:** 378 mUM pts were randomized 2:1 to tebe vs. IC. BOR was assessed by investigators using RECIST v1.1. TBP was permitted until: 1) additional ≥20% increase in tumor burden with absolute increase of ≥5 mm, or 2) unequivocal PD of non-target lesions; or 3) new non-measurable lesions. A Cox model adjusted for baseline covariates and for covariates at time of progression for TBP-eligible pts was used to compare survival post progression between those who did (TBP) and did not receive TBP (non-TBP). Stepwise selection of covariates (using $p < 0.1$ as the entry and staying criterion) was applied. Analysis performed on data cut-off 13Oct2020. **Results:** 183 tebe pts were eligible for TBP per protocol; 60% (109/183) received TBP with median duration of 8 wks. 21% of all tebe doses were administered as TBP. The proportion of pts with new lesions at initial progression (44% vs 57%) and median time to initial progression (2.9 mo vs 2.9 mo) were similar between TBP and non-TBP pts. Pts receiving TBP were more likely to have favorable key prognostic factors at baseline or at time of progression. After adjusting for these differences, a numerical benefit in post-progression OS favoring TBP was observed (HR 0.67, 95% CI [0.38,1.19]). Serial review of radiographic time points identified initial progression of sum of target lesions followed by stabilization for > 3 months after initial progression in some TBP pts. Safety profile during TBP was consistent with that expected for pts established on tebe and no pts experienced an AE leading to treatment discontinuation. **Conclusions:** An OS benefit observed for tebentafusp among mUM patients who have initial radiographic progression demonstrates that RECIST assessment underestimates benefit. In a post-hoc analysis of OS following initial radiographic progression, continued treatment with tebentafusp was associated with numerically longer OS after adjusting for key prognostic variables. Tebentafusp treatment beyond progression was tolerated without new safety signals and, in some patients, was associated with radiological stabilization of sum of target lesions for > 3 months following the initial progression. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9586 **Poster Session**

Randomized phase II study of adjuvant sunitinib or valproic acid in high-risk patients with uveal melanoma: The final analysis of cohort 1.

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Background: Despite successful treatment of primary uveal melanoma (UM), tumors with monosomy 3 and 8q amplification (M3 + 8q amp) or DecisionDx-UM Class 2 have high metastatic death rates. We report the final analysis of Cohort 1 in the randomized phase II clinical trial of 6 months of adjuvant sunitinib or valproic acid (VPA) in high-risk UM patients. **Methods:** High risk for systemic metastasis was defined as the following: A) M3 + 8q amp; B) Class 2. Patients within 6 months of initial treatment of primary UM were randomized 1:1 to receive either sunitinib 25 mg daily or VPA 750 mg daily for 6 consecutive months. The primary endpoint was to evaluate the improvement of 2-year overall survival (OS) rate from 70% (historical references) to 85% in each arm. Secondary endpoints included 1) systemic relapse-free survival (RFS) rate at 18 months, 2) ability to complete adjuvant treatment and, 3) toxicity assessment. **Results:** Eighty-eight patients were included in the final analysis. There were no differences in tumor size or T stage between the two treatment arms. Nine of 45 patients in the sunitinib arm and 4 of 43 patients in the VPA arm could not complete the 6-month treatment due to toxicity (sunitinib n = 6, VPA n = 2) or systemic progression (sunitinib n = 3, VPA n = 2). All but 9 patients (death due to metastasis, sunitinib n =4, VPA n = 5) were followed for at least 2 years. With a median follow-up of 52.6 months, both drugs met the primary end point with 2-year OS rates of 95.6% (sunitinib, 90% CI 86.5-98.6%) and 90.7% (VPA, 90% CI 80.1-95.8%). The 18-month RFS rates were 75.6% (sunitinib, 90% CI 63.1-84.3%) and 62.8% (VPA, 90% CI 49.4-73.5%). Although not statistically significant, there was a trend of superior RFS with sunitinib over VPA in primary UM with T-stage 3-4 (p=0.131) or >12mm (p=0.129). There was no significant difference in median RFS in HLA-A*02:01 positive or negative status (24.6 vs. 24.8 months). It is of note that the potential survival benefit of sunitinib over VPA diminished after 3 years, indicating longer duration of sunitinib administration might be required. In the multivariable Cox analysis, the RFS was not significantly different in the two treatment arms, but increase of tumor diameter was associated with increase hazard of progression (HR=1.23, 95% CI: 1.13, 1.33; p<0.001). **Conclusions:** Six months of adjuvant sunitinib or VPA resulted in 2-year OS of 95.6% and 90.7%, respectively, meeting the primary endpoint of the study. Sunitinib showed a tendency for a better outcome until 3 years after randomization, thus Cohort 2 was created to investigate the safety and prolonged improvement of RFS and OS with 12 months of sunitinib. Additionally, Cohort 3 with adjuvant sunitinib in combination with VPA for 12 months is currently ongoing. The size of primary tumor influenced the survival and should be adjusted for future adjuvant studies. Clinical trial information: NCT02068586. Research Sponsor: Pfizer Inc, Institutional funds at Thomas Jefferson University.

9587 **Poster Session**

The association between mediators of the receptor for advanced glycation end product (RAGE) axis and immune checkpoint inhibitor (ICI)–induced colitis in patients with melanoma.

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Background: Colitis and other gastrointestinal (GI) toxicity are a frequent and occasionally severe form of immune-related adverse events (irAEs) in patients treated with ICIs. To date, no definitive mechanism has been identified, and this area remains an active field of investigation. We hypothesized that activation of the RAGE axis, known to be implicated in inflammatory bowel disease through stimulation of signal transduction targeted by pro-inflammatory RAGE ligands, members of the S100 family and High Mobility Group Box 1 (HMGB1), might be associated with irAE- colitis. **Methods:** We examined sera from 111 advanced melanoma patients prospectively accrued and followed up at NYULH (treated with anti-PD-L1, n = 44; antiCTL4, n = 23; and combination, n = 44). 24 (22%) developed GI toxicity grade >2. Serum biomarkers of the ligand-RAGE pathways, soluble (s)RAGE, endogenous secretory (es)RAGE, S100B, and HMGB1, were measured in the patients' sera during ICI treatment. Multivariable ordinal logistic regression analyses with all grades of GI toxicity as the primary outcome for all the recorded covariates (including serum biomarkers, clinical covariates) were performed. We then used ordinal multivariable logistic regression with stepwise variable selection. Similar analyses with GI toxicity as a binary outcome ((≥grade 1 vs no toxicity) were also conducted. Only those variables that jointly contributed to the odds of developing toxicity were included in the final stepwise model. No adjustments for multiplicity were included. As sRAGE and esRAGE are highly correlated (r = 0.86), esRAGE concentrations were not used in the joint models. **Results:** A significant association between GI toxicity and concentrations of sRAGE and S100B was identified. The final stepwise multivariable logistic model includes only sRAGE and S100B. The odds of having a one level increase in GI toxicity grade increase 1.100 times (95% CI: 1.008, 1.199; p = 0.029) for each unit decrease of sRAGE (= sRAGE/100). The odds of a one level increase in GI toxicity increase 1.059 times (95% CI: 1.004, 1.116; p = 0.035) for each unit increase of S100B (= s100B/100). All other analyses yielded comparable results. In contrast, concentrations of HMGB1 and other clinical covariates, including response and treatment category, were not associated with GI toxicity. **Conclusions:** Mediators of the RAGE axis, specifically sRAGE and S100B, might have a role in GI toxicity in patients receiving ICIs. The ligand-RAGE axis may be a novel target for irAE therapies for patients receiving ICIs to mitigate the severity of GI toxicity. Research Sponsor: None.

9588 **Poster Session**

A qualitative exploration of melanoma awareness and prevention among Latinx and non-Latinx White populations in urban and rural California.

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Background: Melanoma mortality rates remain high among individuals of lower socioeconomic (SES) status, and racial/ethnic minorities, despite rates declining in non-Latinx whites (NLW). To improve understanding about the factors contributing to inequities in melanoma prevention and care, a qualitative exploratory study was conducted in Northern and Southern California regarding awareness, prevention, and early detection of melanoma in lower SES NLW and Latinx populations living in urban and semi-rural areas. **Methods:** Nineteen focus group (n = 176 individuals: 77% female, 59% self-identified Latinx/Hispanic, and 40% Medi-Cal/state insurance recipients) were conducted with adult participants, stratified by race/ethnicity (Latinx, low-income NLW), geography (semi-rural, urban), and language (English and Spanish). The interview topics included: 1) awareness and views of melanoma risk, prevention, and early detection screening practices; 2) acceptability of primary and secondary prevention strategies in their respective community; and 3) barriers and facilitators of engagement in melanoma prevention and care. Using a hybrid inductive and deductive approach, thematic analysis was used for data analysis. Findings were organized within a socioecological model (individual, interpersonal, community and health system/policy level). **Results:** Individual level findings revealed that many participants were not familiar about melanoma yet were willing to learn through trusted sources. Brown or darker skin tones were perceived as having less risk for skin cancer. Interpersonally, social relationships were important influences for individuals practicing skin cancer prevention. However, for several Latinx and semi-rural participants, conversations about melanoma prevention did not occur with family and peers. At the community level, semi-rural participants reported distance or lack of transportation to a clinic as challenges for dermatology care access. Healthcare systems barriers included burdens of additional medical care costs and obtaining dermatology referral. Many participants were in support of health regulations and education that reduce skin cancer risks for outdoor workers and children. **Conclusions:** Varying and intersecting factors influence melanoma awareness, and behaviors associated with knowledge, prevention, and early detection of melanoma in low-income NLW and Latinx individuals and in those living in semi-rural areas. Our findings promote understanding of how barriers across the socioecological spectrum may affect melanoma prevention and early detection particularly among men, individuals of lower socioeconomic status, and Latinx individuals. The study results have implications for health education interventions, which can involve health navigation strategies for individuals and families. Research Sponsor: Mary E. Brenneisen Fund at Stanford Medicine, U.S. National Institutes of Health.

TPS9589 **Poster Session**

Randomized phase 3 trial of IO102-IO103 plus pembrolizumab versus pembrolizumab alone in patients with previously untreated, unresectable, or metastatic melanoma.

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Background: The treatment of melanoma has improved markedly with the emergence of new immune therapies, and both anti-PD-1 monotherapy and the combination of the anti-PD-1 antibody nivolumab and anti-CTLA-4 therapy ipilimumab are now considered standard-of-care in the unresectable or metastatic (advanced) melanoma setting. However, many patients have primary or acquired resistance to these therapies, thereby underpinning the need for more effective approaches. IO102-IO103 is a potentially first-in-class, dual-antigen, immune-modulatory therapy targeting the key cancer immune resistance pathways mediated by IDO and PD-L1. The ability of IO102 and IO103 to respectively activate the specific T cells that recognize these checkpoint molecules and directly modulate immune regulation has previously been demonstrated both preclinically and in human clinical trials. A synergistic anti-tumor response upon treatment against both IDO and PD-L1 has also previously been demonstrated in a preclinical model where IDO and PD-L1 were expressed by different cells in the tumor microenvironment. Due to the distinctive mechanisms of action of IO102-IO103 and anti-PD-1 antibodies, there may be a further synergistic effect when treatment is combined. A previous Phase 1/2 trial investigating the use of IO102-IO103 plus nivolumab in patients with anti-PD-1-naïve metastatic melanoma has demonstrated promising anti-tumor activity with an overall response rate (ORR) of 80%, median progression-free survival (PFS) of 26 months and a manageable safety profile (NCT03047928; Kjeldsen et al, Nat Med 2021). **Methods:** This is a Phase 3, multicenter, open-label, randomized, 2-arm trial investigating the efficacy and safety of IO102-IO103 plus pembrolizumab versus pembrolizumab alone (EudraCT: 2021-004594-32; ClinicalTrials.gov No: NCT05155254). Inclusion criteria include: adult patients with untreated, unresectable (Stage III), or metastatic (Stage IV) melanoma; > 6 months since last dose of (neo)adjuvant treatment with targeted or immune therapy (in those previously treated); and ≥1 measurable lesion by RECIST v1.1. Primary endpoint is PFS by blinded independent central review. Secondary endpoints include ORR, durable response rate, complete response rate, duration of response, time to response, disease control rate, overall survival, and safety/tolerability. Target enrollment is 300 patients at > 100 sites in 20 countries. Patients are randomized 1:1 to receive either pembrolizumab 200 mg intravenously (IV) every 3 weeks up to 2 years or pembrolizumab 200 mg IV every 3 weeks up to 2 years with dual-antigen IO103-IO102 85-85 μg and Montanide adjuvant subcutaneously on Day 1 and 8 of cycle 1 and 2 and on Day 1 of each cycle thereafter. Enrolment for the study is ongoing. Clinical trial information: EudraCT: 2021-004594-32; ClinicalTrials.gov No: NCT05155254. Research Sponsor: IO Biotech ApS & Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS9590 **Poster Session**

First-in-human clinical trial of an oncolytic adenovirus armed with TNFa and IL-2 in patients with advanced melanoma receiving adoptive cell transfer of tumor-infiltrating lymphocytes.

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Background: The long-term complete remission experienced by some cancer patients after receiving immunotherapies, such as adoptively transferred tumor-infiltrating lymphocytes (ACT-TIL), represent the ideal outcome to pursue for the development of therapies for oncology. At the same time, those responses are limited to a minority of treated patients, and adverse events resulting from preconditioning chemotherapy and postconditioning IL2 are a rather common scenario. TILT-123 is an oncolytic adenovirus (Ad5/3-E2F-D24-TNFa-IRES-IL2) designed to enable T-cell therapies and checkpoint inhibition against cancer. Ultimately, the aim of this approach is to expand the proportion of patients benefiting from immunotherapies. Extensive preclinical studies with this technology showed that the virus repolarizes the tumor's immune microenvironment in a way that favors T-cell presence and their activity against tumor cells. When TILT-123 was used together with TILs in preclinical in vivo models, animals had a higher chance to display curative results while showing reduced toxicity as the use of TILT-123 replaces the pre and post conditioning (Havunen R. et al Mol Ther Oncolytics 2016, Santos J.M. Mol Ther 2018). A Phase I clinical trial (NCT04217473) is ongoing to evaluate safety of the approach in advanced melanoma patients. Extensive biological assays of patient aim to characterize viral transduction of tumors through the intravenous and intratumoral routes, and the recruitment of activated lymphocytes to tumors in order to elucidate the immunological impact of the drug. **Methods:** The primary aim of NCT04217473 is to evaluate safety of TILT-123 in advanced melanoma patients. Refractory or recurrent stage III/IV patients, which cannot be treated with curative intent with available therapies, and are eligible for ACT-TIL therapy, can potentially participate in the study. TILT-123 administration begins while the manufacturing of ACT-TILs takes place and continues after the TIL-therapy is administered to the patient. In contrast with standard ACT-TIL therapy, patients are not conditioned with lymphodepletion or IL-2 in this approach. Patients must present at least one biopsiable/operable tumor for the generation of TILs and another injectable lesion for intratumoral administration of TILT-123. The open label, dose escalation trial has the main endpoint of establishing TILT-123 safety by day 36 (prior to TIL administration), which is based on the incidence of adverse events, severe adverse events, vital signs, ECG, and safety laboratory results. Secondary endpoints include safety and tolerability after TIL therapy has been administered, evaluation of antitumor responses and studies of tumor immune repolarization. Cohorts 1-3 have been completed without DLTs. Enrollment in cohort 4 was initiated in December 2021. Clinical trial information: NCT04217473. Research Sponsor: TILT Biotherapeutics Ltd.

TPS9591 **Poster Session**

A phase II study of biomarker-driven early discontinuation of anti–PD-1 therapy in patients with advanced melanoma (PET-Stop): ECOG-ACRIN EA6192.

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Background: In patients (pts) with advanced, metastatic melanoma (aMM) anti-PD-1 monotherapy and anti-PD-1/anti-CTLA-4 combination regimens yield durable responses, yet the optimal therapy duration remains unclear. Most prospective studies have treated responding pts for at least 2 years unless there has been a prohibitive treatment related adverse event (TRAE). Durable treatment-free survival has been observed in pts where anti-PD-1 therapy is discontinued after short courses due to TRAEs. Biomarkers are needed to define which pts may safely discontinue anti-PD-1 therapy in order to reduce financial toxicity and risk of late TRAEs, and to improve quality of life. ^{18}FDG-PET/CT scan and tumor biopsy may better assess for active residual disease and identify pts who can safely discontinue treatment. A retrospective study at G-LCCC demonstrated responding pts with aMM who elected to discontinue their anti-PD-1 therapy (median treatment duration 12 months) after a negative PET/CT scan and/or tumor biopsy had event free survival (EFS) of 95% at 3 years (Gibney et al JITC 2021). We hypothesize that pts with disease control by CT scan after 12 months on anti-PD-1 therapy can be safely discontinued from treatment if no hypermetabolic activity on PET/CT scan or negative biopsy for active disease. **Methods:** EA6192 is a multicenter phase II study to evaluate the EFS after discontinuation of anti-PD-1-based therapy in aMM pts with PET/CT scan and/or biopsy that is negative for active disease. Pts with unresectable stage IIIB-IV aMM treated with nivolumab/ipilimumab (nivo/ipi), nivo, pembrolizumab (pembro), or pembro/ipi are eligible. Pts with uveal melanoma are excluded. Pts must receive 52 weeks of therapy, have disease control (CR, PR or SD by imRECIST) and no prohibitive TRAEs. Eligible pts undergo screening including ^{18}FDG-PET/CT scan at 52 weeks (+/- 2 weeks) from start of anti-PD-1 therapy. Pts with hypermetabolic tumor site(s) undergo biopsy. Pts with non-hypermetabolic PET/CT scan or negative biopsy are assigned to Arm A and are monitored off active treatment. Pts with hypermetabolic PET/CT scan and positive or non-feasible biopsy are assigned to Arm B and remain on active treatment for another 48 weeks. Restaging scans are performed every 12 weeks. Arm B pts with disease control undergo a second PET/CT scan and biopsy, and then are monitored off active treatment. 150 patients are planned for accrual. The primary objective is to accurately define the 12-month EFS rate of Arm A, distinguishing between the null and alternative hypotheses of 12-month EFS rate of 88% and 95% with 92% power and one-sided type 1 error rate of 0.072. Secondary and exploratory objectives include assessment of pathologic response, EFS for Arm B, overall survival, incidence of late TRAEs, and correlative biomarker studies. This study is actively enrolling pts. Clinical trial information: NCT04462406. Research Sponsor: U.S. National Institutes of Health.

TPS9592 **Poster Session**

C-POST protocol update: A phase 3, randomized, double-blind study of adjuvant cemiplimab versus placebo post-surgery and radiation therapy (RT) in patients (pts) with high-risk cutaneous squamous cell carcinoma (CSCC).

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Background: CSCC is the second most common skin cancer with an estimated incidence of 1 million cases per year in the US. While the surgical cure rate for CSCC is > 95%, some pts have high risk of recurrence as assessed by immune status, primary disease stage, extent of nodal involvement, presence of extracapsular extension (ECE), and prior treatment. Postoperative RT is recommended for these pts but relapse with locoregional recurrence or distant metastases may still occur. C-POST is evaluating the efficacy of cemiplimab as adjuvant therapy for pts with high-risk CSCC. Here, we provide summary of the most recent study protocol amendment. **Methods:** C-POST is a randomized, placebo-controlled, double-blind, multicenter Phase 3 study to evaluate cemiplimab as adjuvant treatment for pts with high-risk CSCC, based on surgical and clinicopathologic findings, who completed surgery and postoperative RT (minimum total dose 50Gy, within 10 weeks before randomization) (NCT03969004). Pts with at least one of the following high-risk features are eligible: (1) nodal disease with (a) ECE and at least one node ≥20 mm or (b) at least three lymph nodes positive on surgical pathology report, regardless of ECE; (2) in-transit metastases; (3) T4 lesion; (4) perineural invasion; and (5) recurrent CSCC with at least one other risk factor. Pts with CSCC involvement in at least three lymph nodes (feature 1b) were added to the eligibility criteria, as this group was found to be at similar risk of CSCC recurrence as the initially planned study population. Protocol amendment now allows patients with chronic lymphocytic leukemia (CLL) who are not on active treatment to be enrolled. The study has two parts. In Part 1 (blinded), pts are randomly assigned 1:1 to receive cemiplimab 350 mg or placebo intravenously every 3 weeks for 12 weeks, followed by cemiplimab 700 mg or placebo every 6 weeks for 36 weeks. In optional Part 2 (unblinded), pts in the placebo arm who experience disease recurrence and pts in the cemiplimab arm who experience disease recurrence ≥3 months after completion of 48-week treatment in Part 1 are eligible to receive open-label cemiplimab for up to 96 weeks. The trial is expected to enrol 412 pts from about 100 sites in North and South America, Europe, and Asia-Pacific regions. Key primary objective is to compare disease-free survival; secondary objectives include evaluating overall survival, freedom from locoregional relapse, and distant relapse with adjuvant cemiplimab versus placebo in patients with high-risk CSCC. This study is once again open for enrolment following interruptions owing to the COVID-19 pandemic. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals, Inc., and Sanofi.

TPS9593 **Poster Session**

A randomized, controlled, open-label, phase 2 study of cemiplimab ± RP1 in patients with advanced cutaneous squamous cell carcinoma (CERPASS).

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Background: RP1 is an oncolytic virus (HSV-1) that expresses a fusogenic glycoprotein (GALV-GP R-) and granulocyte macrophage colony stimulating factor (GM-CSF). In preclinical studies, RP1 induced immunogenic tumor cell death and provided potent systemic anti-tumor activity, which is further improved by combining anti-PD-1 therapy. The prognosis for advanced and metastatic cutaneous squamous cell carcinoma (CSCC) remains poor for many patients despite the adoption of cemiplimab and pembrolizumab as a standard treatment. Preliminary results from IGNYTE, a phase I/II clinical study of RP1 in combination with nivolumab showed a high rate of deep and durable responses in patients (pts) with CSCC. This study is evaluating the efficacy and safety of cemiplimab ± RP1 versus cemiplimab alone in advanced CSCC. **Methods:** This global, multicenter, randomized phase 2 study is enrolling pts with metastatic or unresectable, locally advanced CSCC who are not candidates for/refuse surgery and/or radiation therapy. Key eligibility criteria include no prior treatment with anti-PD1/PD-L1 antibodies or oncolytic viruses. The clinical trial is enrolling approximately 180 pts from centers in the EU, Australia, Canada, and USA. Pts are randomized in a 2:1 ratio to receive combination therapy or monotherapy respectively. Pts receive 350 mg of cemiplimab intravenously (IV) Q3W for up to 108 weeks. In the RP1 + cemiplimab arm, RP1 is injected intratumorally at a starting RP1 dose of 1×10^6 plaque-forming units (PFU)/mL alone, followed by up to 7 doses of RP1 at 1×10^7 PFU/mL Q3W together with the same dose of cemiplimab. Pts in the combination arm may receive up to 8 additional RP1 doses if protocol specific criteria are met. No crossover is allowed. Pts are stratified by disease status (nodal or distant metastatic or locally advanced CSCC) and prior systemic therapy. Tumor assessments are performed every 9 weeks. The dual independent primary endpoints are overall response rate and complete response rate, both by a blinded independent review. Secondary endpoints include safety, progression-free survival, duration of response, and overall survival. Exploratory endpoints include quality of life, and immune biomarker analyses. This trial is currently enrolling pts. Clinical trial information: NCT04050436. Research Sponsor: Replimune Group Inc.

TPS9594 **Poster Session**

DELTA-1: A global, multicenter, phase 2 study of ITIL-168, an unrestricted autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in adult patients with advanced cutaneous melanoma.

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Background: Patients (pts) with advanced (unresectable or metastatic) cutaneous melanoma and persistent disease after checkpoint inhibitor therapy have poor outcomes and limited treatment options, highlighting a significant unmet medical need (Schadendorf D et al. *Lancet*. 2018;392:971-984). Investigational autologous TIL cell therapies have shown promise in this population, partly attributable to their intrinsic and patient-specific antitumor activity (Borch TH et al. *J Immunother Cancer*. 2020;8:e000668). Made from each patient's digested and cryopreserved tumor, ITIL-168 is an autologous TIL cell therapy manufactured to offer an unrestricted T-cell receptor repertoire. A single-center, compassionate use clinical series demonstrated the feasibility and clinical utility of an earlier version of ITIL-168, with a high overall response rate among pts previously treated with PD-1 inhibitor (PD-1i) therapy (58%, n = 12; Pillai M et al. *Ann Oncol.* 2021;32[suppl 5]:S882). DELTA-1 (NCT05050006) is a global, multicenter phase 2 study to evaluate efficacy and safety of ITIL-168 in pts with cutaneous melanoma relapsed or refractory to a PD-1i, pts intolerant to a PD-1i, and pts whose current best response to a PD-1i is stable disease. **Methods:** Pts aged ≥18 years with histologically confirmed advanced cutaneous melanoma, ECOG performance status 0-1, and adequate organ function will be enrolled in 1 of 3 cohorts. Cohort 1 (n≈80) will include pts who relapsed after or were refractory to ≥1 prior line of systemic therapy, including a PD-1i and, if *BRAF*-mutated, a BRAFi ± MEKi. Cohorts 2 and 3 (n≈25 each) will include pts intolerant to PD-1i and those with stable disease after ≥4 doses of PD-1i, respectively. After tumor resection for TIL harvest, pts must have ≥1 remaining measurable lesion per RECIST 1.1. Pts with uveal, acral, or mucosal melanoma, prior allogeneic transplant or cell therapy, and with central nervous system (CNS) disorder or symptomatic and/or untreated CNS metastases are ineligible. Pts will receive 5 days of lymphodepleting chemotherapy (cyclophosphamide ×2 days overlapping with fludarabine ×5 days) followed by a single ITIL-168 infusion ($\geq 5 \times 10^9$ cells) and supportive short-course, high-dose IL-2. The primary endpoint is objective response rate (ORR) per central review. Secondary endpoints include duration of response, progression-free survival, overall survival, disease control rate, TIL persistence, and safety. Hypothesis testing of ORR will be performed for cohort 1. The primary analysis will occur when all pts in the cohort 1 modified intent-to-treat population have been followed for ≥6 months after the first posttreatment disease assessment. DELTA-1 opened for enrollment in September 2021. Updated site information will be given at the time of presentation. Clinical trial information: NCT05050006. Research Sponsor: Instil Bio, Inc.

TPS9595 **Poster Session**

Optimization of Voyager V1 (VV1) oncolytic virus systemic delivery in combination with cemiplimab and ipilimumab in patients with melanoma and non–small cell lung cancer (NSCLC).

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Background: There is a need for novel immunotherapies to address the patient population that never or no longer responds to immune checkpoint inhibitors (CPI). VV1 is an oncolytic vesicular stomatitis virus engineered to express human interferon beta (IFNβ) to enhance cellular anti-tumor immune responses and tumor selectivity. Phase 1 studies demonstrated VV1 anti-tumor activity in several malignancies with or without a CPI. We are exploring ways to optimize VV1 efficacy in combination with cemiplimab, an anti-PD1 antibody approved for lung, basal and squamous cell skin cancers. Recent clinical data support a 5-fold higher dose of VV1 than was previously explored, and pre-clinical data show synergy between the oncolytic and an anti-CTLA4 antibody, in addition to cemiplimab, supporting exploration of a triplet. What was originally a five-arm study of intravenous (IV) VV1 in combination with IV cemiplimab has been amended to focus on 2 means of optimizing efficacy: use of a higher dose of VV1 and triplet combination in proof-of-concept populations. **Methods:** We are now enrolling pts with advanced melanoma (after progression on anti-PD1) and plan to include 1st-line NSCLC pts with PD-L1 expression $\geq$50%. The study is first exploring the preliminary anti-tumor activity, safety, and immunogenic activity of the combination of IV VV1 at a dose of 1.0×10^{11} $TCID_{50}$ once on D1 followed by IV cemiplimab Q3W starting on D8, or the same regimen with an additional intratumoral injection of VV1 1.0×10^{9} $TCID_{50}$ once on D1 for pts with accessible lesions. Pts receive IV cemiplimab Q3W until confirmed disease progression or intolerable toxicity. Once at least 6 pts have been treated with acceptable safety across the 2 melanoma doublet cohorts using this higher dose of VV1, a 3rd melanoma cohort will open to add a single dose of ipilimumab 50 mg on D1 (all IV triplet). Once 6 melanoma pts have received the triplet safely, the 1st-line NSCLC cohort will open. All cohort decisions are guided by a Data Review Committee. Cohorts will be expanded based on a Simon 2-stage design using a type I error rate of 0.05 and power of 85%. Null ORR is 10% with a target of 35% for 2nd line melanoma and null ORR is 40% in 1st line NSCLC with a target of 70%. Each melanoma cohort will require a response in $\geq$2 of 10 pts in the 1st stage to add 11 more in the 2nd stage, while NSCLC will first need 5/9 evaluable pts to respond, then an additional 13 to complete the design. Response is assessed at week 7 then Q9W per RECIST v1.1. The study includes serial biopsies in $\geq$3/10 pts in Stage 1 of each of the IV melanoma cohorts (doublet and triplet therapy), all pts in Stage 2 of these IV melanoma cohorts, and all pts in both Stage 1 and Stage 2 of the IV/IT melanoma cohort, to permit a thorough investigation of the impact of the 3 immunotherapies under investigation. The study is currently ongoing in the USA. Clinical trial information: NCT04291105. Research Sponsor: Vyriad and Regeneron.

TPS9596 **Poster Session**

ATTAC-MCC: Phase I/II study of autologous CD8+ and CD4+ transgenic T cells expressing a high affinity MCPyV-specific TCR combined with checkpoint inhibitors and class I MHC-upregulation in patients with metastatic MCC refractory to PD-1 axis blockade.

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Background: Merkel cell carcinoma (MCC) is a highly aggressive skin cancer, with an incidence that has doubled in the last 20 years to approximately 3000 cases/year in the US. Over one-third of patients will develop widespread disease, and survival in these patients has been historically poor with a 5-year survival rate of < 10%. MCC is highly immune-sensitive due to the antigenicity of the cancer-causing Merkel cell polyomavirus (MCPyV) expressed in most MCC tumors. Although immune checkpoint inhibitors (ICIs) targeting the PD-(L)1 axis show promising efficacy, most MCC patients will eventually relapse. There is no standard of care for patients that become refractory to ICIs. We hypothesize that cellular immune therapies targeting MCPyV may provide additional clinical benefit to these patients. To test this, we have engineered high-affinity TCR T cells against MCPyV and initiated a clinical trial. **Methods:** NCT03747484 is an ongoing phase I/II, open label, investigator-initiated trial (IIT) of FH-MCVA2TCR in combination with an anti-PD-(L)1 checkpoint inhibitor and an agent to upregulate MHC-I expression on tumor cells. The trial is conducted in patients aged 18 years or older with metastatic or unresectable, histologically confirmed virus-positive MCC whose disease has progressed on or after treatment with a PD-(L)1 axis checkpoint inhibitor. Patients undergo leukapheresis to collect white blood cells (WBCs) for TCR T cell product manufacturing. The cell product is administered on day 0. Patients receive an agent to upregulate MHC-I on tumor cells and continue on an anti-PD-(L)1 checkpoint inhibitor for up to one year. In phase I, three patients receive up to two infusions of dose level 1 of the T cell product. The primary objectives of phase I are to determine safety and tolerability based on dose-limiting toxicities (DLT) during an observation period of 28 days after the first infusion. Phase II enrolls patients at dose level 2. The total sample size of phase II is 12 patients. The first three patients are enrolled in a staggered manner and observed for DLTs. If no DLTs occur, the remaining sample size is accrued in open enrollment. The main objectives of phase II are safety based on number of adverse events and preliminary efficacy based on tumor response according to RECISTv1.1 and iRECIST. Secondary/exploratory objectives include cellular kinetics of TCR T cells, T cell phenotype, tumor infiltration kinetics, and MHC-I expression dynamics over time. After the first 12 months, patients transition to a long-term follow-up (LTFU) study for up to 15 years as per FDA guidelines. Clinical trial information: NCT03747484. Research Sponsor: Affini-T Therapeutics, Inc.

TPS9597 **Poster Session**

An open-label, multicenter, phase 1b/2 study of RP1, a first-in-class, enhanced potency oncolytic virus in solid organ transplant recipients with advanced cutaneous malignancies (ARTACUS).

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Background: RP1 is an oncolytic virus (HSV-1) that expresses a fusogenic glycoprotein (GALV-GP R-) and granulocyte macrophage colony stimulating factor (GM-CSF). In preclinical studies, RP1 induced immunogenic tumor cell death and provided potent systemic anti-tumor activity. Clinical data in combination with nivolumab has demonstrated a high rate of deep and durable response in patients with advanced skin cancer. Solid organ transplantation (SOT) is an important lifesaving procedure for patients with a wide range of end-organ diseases, but requires patients (pts) to undergo lifelong immunosuppression to prevent allograft rejection, and skin cancers (SCs) – including cutaneous squamous cell carcinoma (CSCC) – are common post-transplant malignancies. SC in SOT pts is generally managed with surgical resection, radiation therapy, and chemotherapy or targeted therapy. The use of immune checkpoint inhibitors in SOT recipients has improved outcomes but is associated with a high risk of allograft rejection. Thus, there is a high unmet need for a safe and effective treatment that also protects pts from allograft rejection. The objective of this study is to assess the safety and efficacy of single-agent RP1 in SOT patients with SCs, with a focus on CSCC. **Methods:** This study will enroll up to 65 evaluable SOT pts with locally advanced or metastatic SCs. The study has two parts. In Part A, pts will receive an initial dose of 1×10^6 plaque-forming units (PFU) of RP1. Two weeks later they will receive 1×10^7 PFU of RP1 and continue every two weeks until pre-specified study endpoints are met. In Part B, after determining the safety and tolerability in the initial cohort with kidney and liver transplants, the study may also enroll heart and lung transplant recipients. RP1 will be administered by intra-tumoral injection, utilizing image guidance as clinically appropriate. Key inclusion criteria are pts with confirmed recurrent, locally advanced or metastatic CSCC and up to 10 pts with non-CSCC SC, stable allograft function and ECOG performance status of ≤ 1. Pts with prior systemic anti-cancer treatment are allowed. Key exclusion criteria are prior treatment with an oncolytic therapy, active herpetic infections or prior complications of HSV-1 infection and a history of organ graft rejection within 12 months. The primary objective of the trial is to assess efficacy determined by objective response rate and safety of single agent RP1. Additional secondary endpoints include duration of response, complete response rate, disease control rate, progression-free survival and overall survival. Clinical trial information: NCT04349436. Research Sponsor: Replimune Group Inc.

TPS9598 **Poster Session**

Early together: A randomized phase III study of early palliative care in metastatic uveal melanoma (MUM).

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Background: Uveal melanoma is a rare cancer. Up to 50% of patients (pts) develop metastasis, mainly hepatic. Overall survival in metastatic pts is 12 months (mo), contrasting with a good overall condition until death. To evaluate the impact of integrating early palliative care on patient needs and self-efficacy, we designed a comparative randomized trial in MUM pts. **Methods:** 162 pts will be randomized (1:2) between the control and the experimental groups in two French centres (Institut Curie-Paris and Centre Antoine Lacassagne-Nice). In the control group, palliative care is introduced according to international guidelines. In the experimental group, it is added earlier, concomitant to the announcement of metastases by the medical oncologist. The main objective is to assess if early supportive care impacts on patient psychological needs at 6 mo, versus standard of care, based on the SCNS-SF34 questionnaire. Secondary objectives include patient's other needs at 6 and 12 mo, quality of life (QLQ-C30), progression-free and overall survival, and partners' needs (SCNS-P&C). MUM pts, suitable for a treatment with no curative intent, ECOG PS 0-1, with no physical or biological sign of disease, and capable of filling questionnaires are eligible. Questionnaires are completed by all pts at each oncological visit (baseline, 3, 6, 9 and 12 mo). Supportive care visits take place every 6 weeks if needed and address patient's information needs, disease and treatment understanding, social and psychological status, symptoms, and partners' involvement. Prognostic uncertainty and disease seriousness in the absence of symptom is addressed depending on pts' expressed needs. Medical oncologists and supportive care physicians from both centres attend communication skill training provided by an expert during the study. Analyses: SCNS-SF34 psychological needs scale scores at 6-mo will be compared with a Student's t-test, in an ITT analysis. For 10 points mean score difference expected between groups (within standard deviation of 20 points) and a two-sided type 1 error of 5%, inclusion of 54 pts (control group) and 108 pts (experimental group) provides the study 85% of power. The planned inclusion period is 3 years, pts will be followed for one year, for a total study duration of 4 years. From July 2020 to January 2022, 63 pts have been enrolled in the trial; 2 pts declined. Five pts were removed early from the study: one for consent retrieval, 4 for early death due to metastasis. COVID-19 delayed enrollment for 5 months. We plan to complete the study Q4 2023 and to analyze the data Q4 2024. Clinical trial information: NCT04728113. Research Sponsor: Cancéropôle Ile-de-France and INCa SHS-E-P 2019 French national grants, Patients donations.

Questionnaires.	
1	Supportive Care Needs Survey (SCNS-SF34)
2	European Organization for Research and Treatment (EORTC) QLQ-C30
3	Hospital Anxiety and Depression Scale (HADS)
4	Prognosis and Treatment Perceptions Questionnaire (PTPQ)
5	Generalized Self-Efficacy scale (GSE)
6	Supportive Care Needs Survey-Partners & Caregivers (SCNS-P& C)

TPS9599 **Poster Session**

A biomarker-guided Bayesian response-adaptive phase II trial for metastatic melanoma: The Personalized Immunotherapy Platform (PIP) trial design.

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Background: Anti-PD1-based immunotherapies have been approved for many cancer types and are now a standard therapy for advanced melanoma. Despite this, ~50% of advanced melanoma patients (pts) fail to respond or eventually progress after response. It is therefore critical to identify pts with a low likelihood of response to anti-PD1-based therapy and efficiently assess activity of rationally-selected alternative novel immunotherapies. **Methods:** We designed this investigator-initiated phase II PIP-Trial to evaluate two consecutive biomarker testing platforms, followed by the activity of rationally selected 5 novel agents in pts with advanced melanoma. Two separate pt populations are included: Part-A) treatment-naïve pts predicted to be resistant to either anti-PD-1 alone or combined with ipilimumab using Biomarker Test-1); and Part-B) pts who had progressed on 1 prior line of PD1-based therapy. Part-A) is a Bayesian adaptive multi-arm multi-stage design using response adaptive randomisation after a burn-in period where pts are randomised to the existing arms with equal probability. From then on, regular interim analyses will be carried out with the objective to either drop poorly performing arms or continue. Part-B) is an open platform without control that combined a selection and an expansion phase to identify best novel agent(s) as second-line therapy. Expansion phase decisions will be based on enrichment for biomarker Test-2. Dropping an arm occurs when the posterior probability of observing a clinically significant effect on the primary outcome (i.e. 6-month RECIST objective response rate (ORR)) is low. The operational characteristics of the design were investigated through simulations considering 4 plausible scenarios with 40% ORR in the control arm (anti-PD1 + Anti-CTLA4). Simulations were based on the upcoming R package BATS. Part-A has at least 85% power to detect a 30% absolute improvement in ORR with respect to the control arm (with a max N = 216 – Table below). Part-B will be able to select two promising treatments in the expansion phase and formally test their efficacy against a minimum ORR of 25% at 80% power (max N = 150). Research Sponsor: The Melanoma Institute Australia, Cancer Institute of New South Wales.

Scenario	Probability of declaring a treatment effective					Average N per arm						Maximum N
	Arm A	Arm B	Arm C	Arm D	Arm E	Control	Arm A	Arm B	Arm C	Arm D	Arm E	
1	0.05	0.04	0.05	0.04	0.04	46	29	28	29	29	29	190
2	0.05	0.05	0.24	0.58	**0.91**	48	25	25	33	40	45	216
3	0.04	0.04	0.04	**0.90**	**0.92**	49	26	25	25	45	46	216
4	0.21	0.21	**0.85**	**0.86**	**0.86**	42	29	29	38	39	39	216

TPS9600 **Poster Session**

Tocilizumab in combination with ipilimumab and nivolumab in solid tumors.

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Background: Immune checkpoint inhibitors (ICIs) are approved for multiple malignancies, however, durable remission rates with ICI monotherapy remains low. Combined treatment with anti-CTLA-4 and anti-PD1 has shown higher response rates in several cancers but is associated with up to 60% grade 3/4 immune-related adverse events (irAEs) leading to frequent treatment discontinuation. The need for corticosteroids to control irAEs may further diminish anti-tumor activity. A multi-disciplinary approach using clinical, preclinical, and translational analyses implicated the IL-6/Th17 axis in both ICI-related autoimmunity and resistance. Further, preliminary data showed that targeting interleukin 6 (IL-6) could be an effective approach to reduce irAEs while maintaining and possibly boosting the antitumor immune response. **Methods:** We are conducting a phase II, open-label, single center study to evaluate the use of combination treatment with tocilizumab (toci; anti-IL6), ipilimumab (ipi; anti-CTLA4) and nivolumab (nivo; anti-PD1) as a front-line therapy for patients (pts) with treatment-naïve advanced cutaneous melanoma (cohort 1), urothelial carcinoma (cohort 2), and EGFR mutant non-small cell lung cancer after tyrosine kinase inhibitors failure (cohort 3) (NCT04940299). Ten pts per disease site will be enrolled, plus an additional 25 melanoma pts in an expansion cohort. Key inclusion criteria are age ≥18 years (yrs) and histologically confirmed locally advanced or metastatic disease, with specific eligibility criteria defined for each cohort. Patients with interstitial lung diseases, autoimmune diseases, infection, or conditions requiring immunosuppressive therapies are not eligible, but stable asymptomatic brain mets are allowed. Ipi/Nivo dosing is as per approved disease indications: in cohort 1 &2, ipi 3 mg/kg + nivo 1 mg/kg is administered intravenously (IV) every 3 weeks (wks) for 4 doses then nivo 480 mg/4 wks up to 2 yrs. In cohort 3, IV ipi 1 mg/kg/6 wks + nivo 3 mg/kg/2 wks is administered up to 2 yrs. In all 3 cohorts, subcutaneous (SQ) toci 162 mg/2wks is administered up to 12 wks. Imaging is every 12 wks up to 2 yrs or until dose-limiting toxicities or progression. The primary outcome is safety/tolerability of the triple therapy. The secondary outcomes are antitumor efficacy and overall survival. Additionally, tumor and blood samples are being collected for longitudinal immune analysis, including gene expression and multiplex histochemistry to identify predictive biomarkers of response, resistance, and toxicity. The trial opened in October 2021 and has enrolled 14 patients to date. Clinical trial information: NCT04940299. Research Sponsor: The University of Texas MD Anderson Cancer Center Prioritizing Research Innovation and Mentoring Excellence Award, Other Foundation.

TPS9601 **Poster Session**

Design and rationale of a first-in-human (FIH) phase 1/1b study evaluating KIN-3248, a next-generation, irreversible (irrev), pan-FGFR inhibitor (FGFRi), in adult patients with solid tumors harboring FGFR2 and/or FGFR3 gene alterations (NCT05242822).

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Background: FGFR1-4 gene alterations are observed in approximately 7% of all human cancers. There are currently 3 FDA-approved, reversible FGFRi for treatment of patients w/previously treated, locally advanced or metastatic (met) cholangiocarcinoma (CCA) harboring FGFR2 gene fusions/rearrangements (pemigatinib and infigratinib) or met urothelial carcinoma (UC) w/susceptible FGFR2 or FGFR3 genetic alterations (erdafitinib). A major limitation of approved and clinical-stage FGFRi is emergence of secondary, on-target resistance mutations (mutn) that reduce duration of response. Up to 67% of CCA patients treated with either reversible or irrev FGFRi exhibit secondary FGFR2 kinase domain resistance mutn at the time of relapse. KIN-3248 is a next-generation, selective, irrev, small molecule pan-FGFRi, structurally designed to inhibit primary FGFR oncogenic alterations as well as secondary kinase domain mutn associated w/disease progression. Preclinically, KIN-3248 has favorable pharmaceutical properties, is well-tolerated with continuous, daily oral administration in 28d GLP toxicology studies in rats and beagle dogs and is efficacious against primary FGFR2 and FGFR3 oncogenic driver alterations as well as secondary FGFR2 resistance mutn (e.g., gatekeeper and molecular brake) in human cancer cell and PDX models *in vitro* and *in vivo*. **Methods:** This is a FIH, multicenter, non-randomized Ph1 study of KIN-3248 in adult pts with advanced & metastatic solid tumors (AMST) harboring FGFR2 and/or FGFR3 gene alterations. KIN-3248 is given po qd continuously in 28-day cycles until drug intolerance or disease progression. Planned sample size is approx. 120 pts: Part A is a dose-escalation to MTD for pts w/AMST having either FGFR2 and/or FGFR3 alterations. Part A assesses single agent KIN-3248; Part B will evaluate a selected dose of KIN-3248 in 3 cohorts of pts (ICC, UC, or other AMST), each driven by specified FGFR alterations. Standard Ph1 enrollment criteria are required (ECOG PS 0-1, normal organ function, prior receipt of standard treatment or medical judgment that such is not appropriate). Pts may have measurable or evaluable disease. Key exclusion criteria include known active brain metastases and active/uncontrolled HBV/HCV. FGFRi-naïve & -pretreated patients are both eligible. Primary endpoints are safety/tolerability (Part A), and preliminary antitumor activity: objective response rate, disease control rate, duration of response, & duration of stable disease (Part B). Secondary objectives include pharmacokinetic and pharmacodynamic assessments including measures of FGFR pathway modulation. Enrollment is expected to commence in April 2022. Clinical trial information: NCT05242822. Research Sponsor: Kinnate Biopharma.

TPS9602 **Poster Session**

Evaluating the impact of perioperative antibiotic prophylaxis on the microbiome in patients with cutaneous malignancy.

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Background: Preoperative antibiotic prophylaxis is commonly used to reduce surgical site infections (SSIs). However, the rate of SSIs following surgical procedures classified as clean is only 2-3%. Overuse of antibiotics is associated with several potential adverse effects, including dysregulation of the gut microbiome. Disruption of the composition and function of the native gut microbiota, referred to as dysbiosis, has been implicated in a number of inflammatory and autoimmune disorders, as well as gastrointestinal (GI) and non-GI cancers. Recent studies have demonstrated that antibiotics have a profound and persistent effect on the gut microbiota, as evidenced by diminished overall abundance and diversity, as well as alteration of community composition that includes a decreased relative abundance of bacteria in the Ruminococcaceae family. In melanoma, diversity of gut microbiota and relative abundance of Ruminococaceae have been linked to improved survival and enhanced response following immune checkpoint blockade. In this study, we seek to determine the impact of preoperative prophylactic antibiotic use on the gut microbiome in patients following surgery for stage I or II melanoma. **Methods:** In this non-comparative randomized pilot trial, the impact of prophylactic antibiotic use at the time of surgical intervention on gut microbiome diversity and composition will be studied. Patients diagnosed with clinical stage I or II melanoma undergoing wide excision with or without lymphatic mapping and sentinel lymph node biopsy are randomized 1:1 to either receive preoperative cefazolin or no preoperative antibiotics. Stool samples and peripheral blood are collected before surgery, the day of surgery (optional), on post-operative day 3 (optional), and 2 weeks and 3 months following surgery. The primary endpoint for the study is change in microbiome alpha diversity at 2 weeks following surgery. Secondary endpoints are change in relative abundance of microbes at 2 weeks and 3 months after surgery and SSI rates according to whether or not prophylactic antibiotics were administered at time of surgery. Exclusion criteria include recent antibiotic use (within 3 months), allergy to beta-lactam or cephalosporin antibiotics, increased risk of infection due to medical comorbidity or use of immunosuppressive medication. Enrollment began in October 2021. As of January 2022, 22 of 30 patients have been accrued to ensure complete sample collection for 20 patients. Study findings may inform a larger trial evaluating interventions to mitigate antibiotic impact. Clinical trial information: NCT04875728. Research Sponsor: None.

TPS9603 **Poster Session**

DETECTION phase II/III trial: Circulating tumor DNA–guided therapy for stage IIB/C melanoma after surgical resection.

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Background: Circulating tumor DNA (ctDNA; the tumor derived fraction of circulating free DNA in the blood) is a well recognized, minimally-invasive biomarker of tumor burden/progression in many cancers. We have previously shown in retrospective and prospective cohorts of patients with melanoma that ctDNA analysis of serial blood samples following curative intent surgery can identify minimal residual disease (MRD) or molecular relapse. The majority of patients with resected stage II melanoma do not recur, therefore better strategies to identify high risk patients are required. Furthermore, a consistent finding in studies of immune therapy in stage IV melanoma is that patients with small volume disease have the best outcome. We aim to test whether early relapse can be identified by ctDNA analysis and acted upon in a clinically relevant timeframe, and if early treatment of molecular recurrence with immune therapy improves outcomes for patients with resected stage IIB/C melanoma. **Methods:** We designed a phase II/III multicenter study across 21 UK and 4 Australian sites with a tumor informed approach employed for ctDNA detection. Droplet digital assays for *BRAF/NRAS/TERT* promoter mutations were validated for sensitive ctDNA detection across two accredited clinical testing laboratories. Patients with stage IIB/C melanoma, *BRAF/NRAS/TERT* promoter mutant cutaneous melanoma, ECOG 0/1, adequate organ function, with complete resection (including sentinel lymph node biopsy) performed within 12 weeks and radiological/clinical disease-free status confirmed within 4 weeks prior to registration, no prior immune/targeted therapy will be followed up with blinded ctDNA sampling in addition to clinical follow-up. Patients with ctDNA detected will be randomised 1:1 in a double blind fashion to continue routine follow-up with investigators choice treatment if they develop disease recurrence, or unblinded and treated with nivolumab 480mg IV Q4-weekly. Primary objectives include i) whether MRD/molecular relapse following curative intent surgery can be identified earlier than clinical relapse, ii) whether early treatment of molecular recurrence with nivolumab improves overall survival. 1050 patients are planned to be enrolled. The study opened in the UK in November 2021 and will open in Australia in Spring 2022. Clinical trial information: NCT04901988. Research Sponsor: Cancer Research UK, Other Government Agency.

TPS9604 **Poster Session**

Confirmatory trial of narrower side margin excision for head and neck basal cell carcinoma in the Japanese (East Asian) population: JCOG2005 (J-BASE-MARGIN).

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Background: Basal cell carcinomas (BCCs), the most common type of skin cancer, frequently occur on the head and neck. Because distant metastases are extremely rare, complete excision with clear margins is the standard treatment for BCCs. In the NCCN Guidelines, the recommended surgical treatment strategies include standard excision with wider margins (> 4 mm) or Mohs surgery or other forms of peripheral and deep en face margin assessment (PDEMA) for head and neck BCCs. However, these strategies are based on studies in the Caucasian population, with BCCs mostly arising as non-pigmented lesions and/or with poorly defined clinical borders. Conversely, in East Asians, most BCCs tend to present as pigmented lesions with well-defined clinical tumor borders. Recent retrospective studies from East Asia have reported positive side margin proportions and local recurrence proportions in BCCs excised with narrower margins that are lower than guidelines-recommended margins. Our previous study investigating 1000 East Asian BCCs also indicated that the estimated positive side margin proportions with 2- and 3-mm surgical margin excision in East Asian BCCs were 3.8% and 1.4%, respectively. Those findings may lead to very limited need for Mohs micrographic surgery or PDEMA in East Asian head and neck BCCs; however, there have been no clinical trials regarding fixed narrower margin excision for those cohorts. **Methods:** This is an investigator-initiated, prospective, multicenter, non-randomized phase III confirmatory trial evaluating the efficacy and safety of narrower surgical margins for the treatment of East Asian patients with head and neck, solitary, primary BCCs with sizes ranging from 3 mm to 20 mm. Eligible patients are aged ≥20 years (≤85 years in men or ≤90 years in women). Narrower margin excisions of 2 mm and 3 mm are applied to BCCs with well-defined clinical borders (cohort A) and poorly defined borders (cohort B), respectively. The primary endpoint is the 5-year local recurrence proportion, and the secondary endpoints are positive side margin proportion and incidence of adverse events. We anticipated an expected 5-year local recurrence proportion of 0.8% in both cohorts and a threshold of 3.3% in cohort A and 4.1% in cohort B. The planned sample size is 410 patients (cohort A, 250; cohort B, 160) to provide a power of 80% with one-sided alpha of 5%, assuming a 5% competing risk of death from other diseases. The planned accrual period is 5 years, and the follow-up period is 10 years; primary analysis will be performed at the completion of 5-year follow-up for all registered patients. The trial began in March 2021, and 225 patients (cohort A, 170; cohort B, 55) have already been enrolled as of January 2022. Clinical trial information: UMIN000043511. Research Sponsor: Japan Agency for Medical Research and Development, Other Foundation.

TPS9605 **Poster Session**

The NADINA trial: A multicenter, randomised, phase 3 trial comparing the efficacy of neoadjuvant ipilimumab plus nivolumab with standard adjuvant nivolumab in macroscopic resectable stage III melanoma.

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Background: Adjuvant treatment with anti-PD1 therapy improves the recurrence free survival (RFS) in resectable stage III melanoma. The Checkmate-238 and KEYNOTE-054 trials respectively reported a 4-year RFS of 52.5% for adjuvant nivolumab and a 3-year RFS of 63.7% for adjuvant pembrolizumab. Despite these improved outcomes, a considerable proportion of patients have a relapse in the years after therapeutic lymph node dissection (TLND). The OpACIN trial showed that neoadjuvant treatment with nivolumab (NIVO) plus ipilimumab (IPI) is feasible and induces a stronger and broader T-cell response. The subsequent OpACIN-neo trial identified 2 cycles of NIVO 3mg/kg + IPI 1mg/kg as a neoadjuvant dosing scheme with decreased toxicity and preserved high pathologic response rates (77%), which was confirmed in the PRADO trial. A favorable 2-year RFS (83,6%) was achieved in the overall OpACIN-neo population, although patients with a pathological partial or non-response have a worse prognosis and may therefore benefit from additional adjuvant therapy. The efficacy of neoadjuvant checkpoint inhibition versus the current standard of adjuvant therapy needs to be confirmed in a phase III trial, before neoadjuvant therapy can be considered as a standard option for this patient population.
Methods: This international, randomized phase 3 trial aims to compare the efficacy of neoadjuvant IPI + NIVO with adjuvant NIVO in macroscopic stage III melanoma. In total 420 patients diagnosed with recurrent or de novo melanoma, with at least one pathologically proven, clinically detectable lymph node (up to 3 in-transit metastases (ITMs) allowed), will be randomized to neoadjuvant or adjuvant treatment. The population will be stratified by BRAF mutation, continent and the presence of ITMs. Patients in arm A will receive 2 cycles of IPI 80mg + NIVO 240mg and will undergo TLND at week 6. In the case of pathological partial response or non-response, surgery will be followed by adjuvant NIVO (11 cycles) or adjuvant dabrafenib + trametinib (46 weeks) if BRAFV600-mutation is present. Patients in arm B will undergo upfront TLND followed by 12 cycles of NIVO 480mg. The primary endpoint will be the event free survival (EFS) defined as the time from randomization until progression to unresectable stage III or stage IV melanoma, recurrent melanoma, a new primary melanoma or death due to melanoma or treatment. Final analysis will be performed after 132 events have been observed, or at latest 2 years after the last patient is included. Baseline biopsies and blood samples (screening, week 0, 3, 6, 9 and 12) will be collected for translational research. Quality of Life questionnaires and electronic Patient Reported Outcomes will be collected using the Kaiku application. The first patient was enrolled on the 23rd of July 2021. Clinical trial information: NCT04949113. Research Sponsor: Bristol Myers Squibb, Other Government Agency.

TPS9606 **Poster Session**

MERLIN_001: A prospective registry study of a primary melanoma gene-signature to predict sentinel node (SN) status and determine its prognostic value for more accurate staging of patients with SN-negative melanoma.

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Background: For patients with cutaneous melanoma, sentinel lymph node biopsy (SLNB) provides important staging and prognostic information that guides surveillance and adjuvant systemic therapy decisions. At most centers, SLNB is indicated for patients with cutaneous melanoma with at least a 5% risk of having nodal metastases, typically melanomas ≥ 0.8 mm in thickness or thinner lesions with high-risk features such as elevated mitotic rate and/or ulceration. SLNB, generally involving a separate incision, does carry a small but measurable risk of complications including seroma, infection and rarely lymphedema, and most patients have negative sentinel lymph nodes. Currently, there is an unmet clinical need to identify patients who may safely forgo SLNB due to a low (<5%) risk of nodal metastasis, who otherwise meet established criteria for SLNB. Previously, a model consisting of gene expression profile (GEP) of the primary tumor combined with clinicopathological features (CP) has been developed to identify melanoma patients with a low risk of having a positive SLNB. The model has also been validated in multiple retrospective studies. The aim of the MERLIN_001 registry study is to prospectively validate the CP-GEP model in an independent multicenter cohort of primary cutaneous melanoma patients who undergo SLNB for standard indications. **Methods:** In the next two years, a total of 10 centers across the US will enroll 2,340 patients with clinically node-negative cutaneous melanoma undergoing SLNB using current guideline indications and will follow these patients for 5 years (ClinicalTrials.gov identifier: NCT04759781). Enrollment of patients started in September 2021 and 242 patients have been enrolled as of February 1, 2022. FFPE material from the initial melanoma biopsy will be used to assess the GEP of the primary melanoma. The CP-GEP probability scores will be expressed as a binary classification (Low Risk or High Risk for nodal metastasis) and will be compared to SLN pathology. Performance metrics for CP-GEP will be evaluated and will include: Negative Predictive Value, Positive Predictive Value, Sensitivity and Specificity, and the corresponding 95% confidence intervals. Risk for nodal metastasis will be calculated for Low Risk and High Risk CP-GEP patients. Finally, the performance of CP-GEP to stratify patients according to risk of recurrence (local, regional, distant, death) will also be studied, since data will be collected for up to 5 yrs. Clinical trial information: NCT04759781. Research Sponsor: SkylineDx B.V.

TPS9607 **Poster Session**

Neo-adjuvant T-VEC plus nivolumab combination therapy for resectable early-stage or metastatic (IIIB-IVM1a) melanoma with injectable disease: The NIVEC trial.

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Background: The prognosis of patients with melanoma is significantly correlated with disease stage and has greatly improved with the introduction of the currently approved therapies. Trials investigating neo-adjuvant treatment with immune checkpoint inhibitors (ICI) have shown high pathologic response rates up to 25-80%, however, still a large group of patients derive no (durable) clinical benefit. Treatment with talimogene laherparepvec (T-VEC), a modified herpes simplex virus type-1, is approved for patients with unresectable stage IIIB-IVM1a melanoma, with high and durable response rates and a mild toxicity profile. Earlier trials have suggested that T-VEC has the capacity to heighten the immune response and to elicit an abscopal effect in melanoma when given in combination with ICI. Combination ICI and intralesional T-VEC has already been investigated in patients with unresectable stage IIIB-IV disease, however, no data is available yet on the potential benefit of this combination therapy in neo-adjuvant setting. This is the first trial investigating the efficacy and safety of neo-adjuvant treatment of T-VEC in combination with nivolumab (anti-PD-1 antibody), followed by surgical resection in patients with resectable stage IIIB-IVM1a melanoma, with the potential of high pathologic response rates and acceptable toxicity. **Methods:** In this single center, single arm, phase II study, a total of 24 patients ≥18 years of age and a good clinical performance score with treatment naïve, stage IIIB-IVM1a melanoma (AJCC 8th edition) with injectable disease and resectable (sub)cutaneous satellite or in-transit metastases and/or tumor positive lymph nodes, will be included. Patients will receive four courses of T-VEC up to 4mL (first dose as seroconversion dose) and three doses of nivolumab (240mg flatdose) every two weeks, followed by surgical resection in week nine. The primary endpoint of this trial is pathologic response rate, with the aim to show a high major pathologic (near-complete or complete) response rate up to 45%. Secondary endpoints are safety according to CTCAE v5.0, the rate of delay of surgery and event free survival. Additionally, prognostic and predictive biomarker research and health-related quality of life evaluation will be performed. Enrollment started in June 2020 in the Netherlands Cancer Institute, with currently 13 of the 24 planned patients treated. Clinical trial information: NCT04330430. Research Sponsor: Amgen Inc.

TPS9608 **Poster Session**

A first-in-human, phase 1b study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of neoadjuvant use of ph-762 administered intratumorally in subjects with advanced melanoma.

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Background: Antibodies targeting immune checkpoints such as PD-1 and CTLA-4 has shown significant benefit in late-stage melanoma. But further improvements in therapeutic options are still required. Two approaches for improving the outcome of immunotherapy with checkpoint inhibitors are neoadjuvant treatment and local intratumoral (IT) injection. IT immunotherapy uses the tumor as its own vaccine to activate the immune system, priming an anti-tumor immune response and generating systemic tumor responses, whilst minimizing systemic exposure and off-target toxicities. Neoadjuvant therapy provides the opportunity for preoperative disease shrinkage with the potential to improve surgical morbidity. There is currently no neoadjuvant standard of care for resectable, advanced melanoma patients. PH-762 is a potent RNAi molecule targeting PD-1 with structural and chemical modifications conferring properties suitable for IT administration, including an optimized cell and tissue uptake profile. Pharmacology studies show potent *in vitro* silencing of PD-1 associated with T cell activation, and robust, dose-dependent *in vivo* inhibition of tumor growth in syngeneic tumor models. **Methods:** The purpose of this study is to evaluate the safety of neoadjuvant use of PH-762 administered by IT injection in subjects with resectable stage IIIB/IIIC/IIID or IV melanoma, to determine the recommended Phase 2 dose, PK after IT injection, and potential immunologic and pathologic tumor responses. Study treatment constitutes of once weekly injections with PH-762 into one designated tumor lesion for 4 weeks prior to surgical excision at 5-6 weeks after the initial injection, with up to 5 dose levels tested in a serial fashion in cohorts of 3 or more subjects. Eligible subjects will have at least one resectable melanoma deposit that is large enough to allow IT injection, and that can undergo repeated biopsy. Subjects with active brain metastases, leptomeningeal disease, uveal melanoma, and auto-immune disease are excluded. The dose of PH-762 will be normalized to tumor volume to ensure an equivalent local dose (tumor tissue concentration). Post tumor excision, subjects will be followed-up for 6 weeks. Primary endpoint is to determine a safe dose of PH-762 assessed by incidence of Dose Limiting Toxicities (DLT) prior to tumor resection. Bayesian optimal interval (BOIN) design will be employed to evaluate escalating doses of PH-762 to determine the Maximum Tolerated Dose based on occurrence of DLT. Tumor changes will be evaluated per RECIST criteria (version 1.1 and iRECIST version adapted for use with IT therapy) and pathological response. Immunological response in tumor tissue and blood samples will be assessed as secondary endpoints. Enrollment commenced in February 2022. Clinical trial information: 2021-002859-10. Research Sponsor: Phio Pharmaceutical.

TPS9609 **Poster Session**

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

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Background: Despite improved outcomes for melanoma patients with the introduction of checkpoint inhibitors (CPIs), ~50% of patients do not respond. A subset of responders ultimately progress and have limited treatment options, underscoring a high unmet need for novel treatments with durable benefit. Patients with mucosal melanoma exhibit response rates and progression-free survival times ~2 times lower than those with cutaneous melanoma. Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds the intermediate-affinity interleukin-2 receptor complex to preferentially activate $CD8^+$ T and NK cells with minimal expansion of regulatory T cells. Nemvaleukin has been granted Orphan Drug designation for the treatment of mucosal melanoma by the FDA. In ARTISTRY-1, the intravenous (IV) recommended phase 2 dose (RP2D) of 6 μg/kg nemvaleukin monotherapy demonstrated durable antitumor activity in patients with advanced melanoma, including mucosal melanoma, previously treated with a CPI. In ARTISTRY-2, the subcutaneous (SC) RP2D of 3 mg q7d was identified demonstrating pharmacodynamic effects consistent with IV delivery. Data support further evaluation of nemvaleukin monotherapy among patients with advanced mucosal and cutaneous melanoma. **Methods:** ARTISTRY-6 is a phase 2, global, multicenter, open-label study. Eligible patients have had prior treatment with an anti–PD-(L)1 therapy with or without anti–CTLA-4 therapy and have an ECOG performance status of 0 or 1 and adequate hematologic reserve and hepatic and renal function. Patients with advanced cutaneous (Cohort 1) and mucosal (Cohort 2) melanoma will receive nemvaleukin at the SC and IV RP2D, respectively. Patients will receive nemvaleukin until progression or intolerable toxicity. The primary objective is to evaluate the antitumor activity of nemvaleukin monotherapy defined by overall response rate. Additional objectives include the evaluation of safety, health-related quality of life, predictive biomarkers, pharmacokinetics, immunogenicity, and pharmacodynamic effects. Clinical trial information: NCT04830124. Research Sponsor: Alkermes, Inc.

TPS9610 **Poster Session**

Capturing uveal melanoma (UM) global practice patterns and clinical outcomes in the collaborative ocular melanoma natural history (OMNi) study (NCT04588662).

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Background: Geographical differences in the management of primary UM, surveillance for recurrence, and care of metastatic disease have emerged based upon local expertise, treatment availability and insurance coverage. We have initiated accrual to OMNi (NCT04588662), an ambispective database developed to provide contemporary real-world data of UM, capturing its natural history and serving as a virtual biospecimen repository. The overall objectives of OMNi are to characterize regional/international UM management practice patterns and associated clinical outcomes in an effort to inform best practice recommendations. **Methods:** OMNi utilizes the Pulse Infoframe Healthie platform, a globally compliant platform which enables the structured collection of data mapped to Observational Medical Outcomes Partnership. The data fields created permit longitudinal capture of data including baseline patient and tumor characteristics, treatment of primary lesion and outcomes, surveillance patterns, time to disease recurrence, treatment of recurrent disease with outcomes, and survival. Inclusion criteria include a diagnosis of uveal melanoma and the ability to provide written informed consent for participation in the prospective registry or an institutional waiver by the IRB/ethics committee for retrospective data collection without written informed consent. We have initiated data collection at 3 US and 3 Australian centers, with 184 patients enrolled to date. Based upon feasibility assessment, we anticipate retrospective data entry for ~2,000 patients and annual recruitment of ~700 patients once all centers are active. Data collected in this OMNi collaboration, which will include additional US, UK and Australian sites, will facilitate new insights, hypothesis testing, as well as clinical trial development and conduct, and through a governance structure, will be made accessible for research. The OMNi dataset can serve and aid in interpretation of clinical trial outcomes in the real-world, facilitate cutting-edge research, and accelerate the development of diagnostics and therapeutics. Clinical trial information: NCT04588662. Research Sponsor: Immunocore and BMS.