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MELANOMA AND OTHER SKIN TUMOURS

1036O Relatlimab (RELA) + nivolumab (NIVO) vs. NIVO in previously untreated metastatic or unresectable melanoma: Additional efficacy in RELATIVITY-047

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Background: RELATIVITY-047 (NCT03470922) evaluated RELA (a LAG-3-blocking antibody) + NIVO as a fixed-dose combination (FDC) vs NIVO in pts with advanced melanoma. The FDC demonstrated superior progression-free survival (PFS) by blinded independent central review in the intent-to-treat (ITT) population with a well-tolerated safety profile and no unexpected safety signals. In this exploratory analysis, we describe the potential benefit in subgroups and beyond initial treatment.

Methods: Pts in RELATIVITY-047 were randomized 1:1 to RELA 160 mg + NIVO 480 mg FDC or NIVO monotherapy 480 mg intravenously every 4 weeks. Treatment continued until progression, unacceptable toxicity, or withdrawal of consent. PFS was assessed across subgroups. PFS2 was defined as the time from randomization to progression on subsequent therapy or death per investigator assessment. Treatment-free time from last study dose to subsequent therapy was also assessed.

Results: 714 pts were randomized to RELA + NIVO FDC (n = 355) or NIVO (n = 359). RELA + NIVO FDC extended PFS across prespecified subgroups, including BRAF, AJCC v8 M stage, and LDH. Median treatment duration was 5.6 mo for RELA + NIVO FDC and 4.9 mo for NIVO and 237 (66.8%) and 233 pts (64.9%), respectively, discontinued treatment, mainly due to disease progression (36.3% vs 46.0%). Pts receiving subsequent systemic therapy in RELA + NIVO FDC and NIVO were 27.9% and 29.8%, respectively, including PD-1 or CTLA-4 inhibitors (9.0% vs 12.8%) and BRAF/MEK therapies (11.5% vs 13.9%). PFS2 favored RELA + NIVO FDC with a median not reached (95% CI 21.8—NA) vs 20.0 mo (95% CI 15.4—25.1) for NIVO (hazard ratio [HR] 0.77 [95% CI 0.61—0.97]). Median treatment-free time from last study dose to subsequent therapy was 3.98 mo (95% CI 2.10—7.43) for RELA + NIVO FDC vs 1.45 mo (95% CI 1.25—1.71) for NIVO (HR 0.63 [95% CI 0.48—0.83]).

Conclusions: RELA + NIVO FDC had demonstrated prolonged PFS in ITT and subgroups of pts with previously untreated metastatic or unresectable melanoma. Pts on RELA + NIVO FDC had enduring benefit beyond initial treatment and prolonged benefit beyond first progression, including longer time to initiation of subsequent treatment.

Clinical trial identification: NCT03470922.

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1037O MASTERKEY-265: A phase III, randomized, placebo (Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage IIIB–IVM1c melanoma (MEL)

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Background: In the phase Ib part of MASTERKEY-265, T + P showed promising complete response rate (CRR) of 33% in 21 patients (pts) with advanced MEL. Here we report efficacy and safety from the phase III, randomized, double-blind MASTERKEY-265/KEYNOTE-034 study of T + P vs Pbo + P in pts with stage IIIB–IVM1c MEL (NCT02263508).

Methods: Unresectable stage IIIB-IVM1c, anti-PD-1 naïve, MEL pts with injectable lesions were randomized 1:1 to T + P or Pbo + P. T was given at $\leq 4 \times 10^6$ PFU followed by $\leq 4 \times 10^8$ PFU 3 weeks later and Q2W until dose 5, and Q3W thereafter. P was given IV 200 mg Q3W. Dual primary endpoints were progression-free survival (PFS) per mRECIST 1.1 by blinded independent central review and overall survival (OS). Secondary endpoints included objective response rate (ORR), complete response rate (CRR), durable response rate (DRR), duration of response (DOR), and safety. Results reported here are the primary PFS and interim OS analyses (data cutoff [DCO] PFS Mar 2, 2020; OS Sep 29, 2020).

Results: A total of 692 pts were randomized (346 to T + P, 346 to Pbo + P); as of the OS DCO, all pts were off study treatment (tx). Median follow-up was 31.0 mo (range: 0.3, 53.0). 6.9% had stage IVM1c disease, 32.7% had LDH $>$ ULN, and 64.9% had PD-L1+ status. Median PFS was 14.3 mo (range: 10.3, 22.1) for the T + P arm and 8.5 mo (range: 5.7, 13.5) for the Pbo + P arm (HR 0.86, 95% CI 0.71, 1.04, $P = 0.13$). Median OS was not reached for the T + P arm and 49.2 mo (range: 40.6, NE) for the Pbo + P arm (HR 0.96, 95% CI 0.76, 1.24, $P = 0.74$). OS was not expected to achieve statistical significance at the primary OS analysis. ORR was 48.6% for the T + P arm (CRR 17.9%) and 41.3% for the Pbo + P arm (CRR 11.6%). DRR was 42.2% in the T + P arm and 34.1% for the Pbo + P arm. There was no difference in DOR between arms ($P = 0.87$, HR [95% CI] 1.04 [0.67, 1.60]). Gr 3+ TEAEs occurred in 161 (46.7%) pts receiving T + P and in 151 (44.0%) pts receiving Pbo + P. Gr 3+ tx-related AEs (TRAEs) occurred in 73 (21.2%) pts receiving T + P and in 55 (16%) pts receiving Pbo + P.

Conclusions: T + P did not significantly improve PFS or OS vs Pbo + P. There was a 5.8 mo numeric difference in PFS between arms. Safety results of T + P were acceptable and consistent with the known safety profiles of each agent.

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1040O Phase II trial of ipilimumab, nivolumab and tocilizumab for unresectable metastatic melanoma

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Background: Immunotherapy with ipilimumab and nivolumab has response rates of 45-55%, but 50% of patients (pts) suffer grade 3-5 immune-related adverse events. High serum IL-6 is associated with a poor outcome with checkpoint inhibition and with short survival in many cancers. Tocilizumab is a humanized IL-6 receptor blocking antibody approved for several arthritides and cytokine release syndrome. In anecdotal cases it reverses steroid-resistant colitis and other immune toxicities. To assess if tocilizumab could reduce toxicity and/or augment efficacy of checkpoint inhibition, a phase II trial of ipilimumab, nivolumab and tocilizumab was performed. Results from the first stage of the trial are reported.

Methods: In this Simon two-stage design phase II study, eligible pts had untreated unresectable/metastatic melanoma. Adjuvant therapy was permitted. Ipilimumumab at 1 mg/kg, and nivolumab at 3 mg/kg were administered intravenously (IV) every 3 weeks (wks), 4 times during induction, then nivolumab maintenance is given for up to 2 years. Tocilizumab was given at 4 mg/kg every 6 wks IV during the first 24 wks. In stage 1 >/= 11 responses in 18 were required and/or less than 6 pts with grade 3-5 irAEs to proceed to stage 2 to total 67 pts.

Results: Twenty-eight pts have started therapy including 14 men and 14 women with a median age of 67. Twenty had ECOG PS 1, and 8 PS 0. Twenty-four pts had stage IV and 4 stage IIIc/d disease. There were 5 grade 3-4 irAEs with one each with enteritis, colitis and nephritis and two with trasaminitis. At 6 months of median follow up, there are 14 RECIST responses of 20 pts (70% ORR) with at least one evaluation at week 12. Two pts are stable at 18 weeks. No responder or stable pts have progressed. Four pts progressed, and two died. Correlative marker studies by serum Luminex assay showed that higher levels of baseline TNF-alpha were associated with grade 3-4 toxicity, and elevated IL-6/IL-8 and C5a at week 7 were associated with progression.

Conclusions: Flipped dose IPI/NIVO with TOCI has promising anti-tumor activity with a favorable toxicity profile. Incidence of grade 3/4 irAEs was 25%. High baseline TNF-a was associated with grade 3/4 irAEs, and elevated week 7 IL-6/IL-8/C5a were associated with progression. Further correlative studies will be presented.

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Legal entity responsible for the study: NYU Grossman School of Medicine.

Funding: Bristol-Myers Squibb.

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1038MO Intracranial activity of encorafenib and binimetinib followed by radiotherapy in patients with BRAF mutated melanoma and brain metastasis: Preliminary results of the GEM1802/EBRAIN-MEL phase II clinical trial

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Background: Systemic treatment for patients (pts) with *BRAF*- mutated (mut) melanoma (mel) and brain metastasis (BMs) include immunotherapy and targeted therapy. COMBI-MB clinical trial analyzed the role of dabrafenib + trametinib, with an intracranial response rate (icRR) of 58% for asymptomatic and 59% for symptomatic pts. Encorafenib + binimetinib (EB) has not been prospectively evaluated in this scenario.

Methods: GEM1802 (NCT03898908) is a prospective phase II clinical trial that evaluates EB (450 mg pd E + 45 mg bd B) in pts with BMs during 56 days (d) followed by brain radiotherapy (RDT) and EB until disease progression. Two cohorts (C) were planned: C1 (N=48), asymptomatic pts; and C2, symptomatic pts (N=15). Primary endpoint is icRR after 56d of EB (before RDT) in C1. Secondary endpoints are extracranial RR, intracranial progression free survival (icPFS), PFS, overall survival and safety. In addition, this study will explore if RDT could improve the duration of response with EB.

Results: We report preliminary results of icRR for first 25 pts with response evaluation after 56d of EB. 14 pts from C1 and 11 from C2 were evaluable for this analysis. icRR was 64.3% and 63.6% in C1 and C2 respectively. Partial response (PR), complete response (CR), stable disease (SD) and progressive disease (PD) as well as G3-4 AEs are described in the table. 71.4% pts in C1 and 72.7% in C2 received RDT following first 56 days of EB.

Table: 1038MO

			C1 (asymptomatic)	C2 (symptomatic)
N			14	11
Previous systemic treatment (%)			21.4	18.2
Brain Target Tumor Burden (mean, mm)			34.5	54.3
%	Number of BMs	1	50	27.3
		2-3	42.8	45.5
		>3	7.1	27.3
	Extracranial disease		85.7	100
	icRR (95% CI)		64.3 (35-87)	63.6 (31-89)
	PR		57.1	54.5
	CR		7.1	9.1
	SD		35.7	36.4
	PD		0	0
	6 month icPFS		70.1	64.3
	Whole brain RDT		28.6	45.5
	Radiosurgery/SBRT		50	33.3
	Related G3-4 AEs		23.5	13.3

Conclusions: These results are in line with previous data reported for other targeted therapies in this setting, demonstrating a high response rate that is independent of symptomatic status of the pts. Based on this analysis, planned enrollment will continue until completion of accrual.

Clinical trial identification: NCT03898908.

Legal entity responsible for the study: Spanish Melanoma Group (GEM).

Funding: Pierre Fabre.

Disclosure: I. Marquez-Rodas: Financial Interests, Personal, Advisory Board: BMS; Financial Interests, Personal, Advisory Board: MSD; Financial Interests, Personal, Advisory Board: Novartis; Financial Interests, Personal, Advisory Board: Pierre Fabre; Financial Interests, Personal, Advisory Board: Roche; Financial Interests, Personal, Advisory Board: GSK; Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Advisory Board: Celgene; Financial Interests, Personal, Advisory Board: Regeneron; Financial Interests, Personal, Advisory Board: Sanofi; Financial Interests, Personal, Advisory Board: Merck Serono; Financial Interests, Personal, Advisory Board: Highligth Therapeutics; Financial Interests, Personal, Advisory Board: Bioline Rx; Financial Interests, Personal and Institutional, Invited Speaker, GEM1802 clinical trial: Pierre Fabre; Financial Interests, Institutional, Invited Speaker, GEM1801 clinical study: Novartis; Financial Interests, Institutional, Invited Speaker, GEM1801 clinical study: BMS; Financial Interests, Institutional, Invited Speaker, GEM1801 clinical study: Roche; Financial Interests, Institutional, Invited Speaker, GEM1801 clinical study: Pierre Fabre; Financial Interests, Institutional, Invited Speaker, GEM1801 clinical study: Incyte; Financial Interests, Institutional, Invited Speaker, GEM1801 clinical study: MSD; Financial Interests, Institutional, Invited Speaker, National coordinator of Spotlight 203 clinical trial: Highlight Therapeutics; Non-Financial Interests, Invited Speaker: Spanish Melanoma Group. 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1039MO CheckMate 204: 3-year outcomes of treatment with combination nivolumab (NIVO) plus ipilimumab (IPI) for patients (pts) with active melanoma brain metastases (MBM)

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Background: In CheckMate 204, asymptomatic pts (cohort A) with active, untreated MBM achieved high intracranial (IC) and extracranial (EC) response rates with NIVO + IPI; efficacy was lower in pts with symptomatic and/or steroid-requiring MBM (cohort B). Here, we report 3-y response and survival outcomes in both cohorts, along with first results of the blinded independent central review (BICR) of imaging data.

Methods: In this open-label, multicenter, phase II study, pts with metastatic melanoma and $\geq$ 1 nonirradiated brain metastasis 0.5—3 cm in diameter received NIVO 1 mg/kg + IPI 3 mg/kg Q3W $\times$ 4, followed by NIVO 3 mg/kg Q2W until progression or unacceptable toxicity. The primary endpoint was IC clinical benefit rate, defined as the proportion of pts with complete response (CR), partial response (PR), or stable disease (SD) $\geq$ 6 mo (per modified RECIST 1.1). Investigator (INV)-assessed and BICR-assessed response and PFS were evaluated along with OS.

Results: At an overall minimum follow-up of 34 mo (median follow-up: 34 mo, cohort A; 7.5 mo, cohort B), there were 101 INV-assessed asymptomatic pts (95 BICR-evaluable) and 18 symptomatic pts (17 BICR-evaluable). INV- and BICR-response rates were consistent (table), with a concordance rate among evaluable pts of 85% for cohort A and 94% for cohort B. For cohort A, 36-mo IC progression-free survival (PFS) was 54% (95% CI, 43—64) by INV and 52% (41—62) by BICR, and overall survival (OS) was 72% (62—80). For cohort B, 36-mo IC PFS was 19% (95% CI, 5—40) by INV and 28% (10—50) by BICR, and OS was 37% (14—60). No new safety signals or treatment-related deaths were reported.

Conclusions: High concordance was observed between INV- and BICR-assessed responses in this trial for both cohorts. The durable 3-y OS and PFS rates for the asymptomatic cohort support the use of first-line NIVO + IPI. Symptomatic pts with MBM remain difficult to treat, but some can derive long-term benefit from NIVO + IPI.

Table: 1039MO

	INV			BICR		
	IC	EC	Global	IC	EC	Global
Asymptomatic, n (%)	N = 101			N = 101[a]		
CR	33 (33)	16 (16)	17 (17)	26 (26)	14 (14)	11 (11)
PR	21 (21)	33 (33)	35 (35)	24 (24)	36 (36)	38 (38)
SD $\geq$ 6 mo	4 (4)	5 (5)	4 (4)	4 (4)	5 (5)	3 (3)
ORR, n (%; 95% CI)	54 (54; 43—64)	49 (49; 38—59)	52 (51; 41—62)	50 (50; 39—60)	50 (50; 39—60)	49 (49; 38—59)
Symptomatic, n (%)	N = 18			N = 18[a]		
CR	3 (17)	1 (6)	1 (6)	3 (17)	2 (11)	2 (11)
PR	0	3 (17)	3 (17)	1 (6)	2 (11)	2 (11)
SD $\geq$ 6 mo	0	0	0	0	0	0
ORR, n (%; 95% CI)	3 (17; 4—41)	4 (22; 6—48)	4 (22; 6—48)	4 (22; 6—48)	4 (22; 6—48)	4 (22; 6—48)

[a]Total patients includes 6 asymptomatic pts and 1 symptomatic pt for whom BICR data were not available. CI, confidence interval; ORR, objective response rate.

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1041MO 5-year update on COLUMBUS: A randomized phase III trial of encorafenib (enco) + binimetinib (bini) versus enco or vemurafenib (vem) in patients (pts) with BRAF V600-mutant melanoma

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Background: Combined BRAF/MEK inhibitor therapy has demonstrated benefits on progression-free survival (PFS) and overall survival (OS) and is standard of care for the treatment (tx) of advanced *BRAF* V600-mutant (*BRAF*^{V600}) melanoma. Here we report additional data from the 5-year update of the ongoing COLUMBUS trial.

Methods: In COLUMBUS Part 1, 577 pts with advanced/metastatic *BRAF*^{V600} melanoma, untreated or progressed after first-line immunotherapy, were randomized 1:1:1 to enco 450 mg once daily + bini 45 mg twice daily, enco 300 mg once daily, or vem 960 mg twice daily. An updated analysis was conducted after 65 months' minimum follow-up. Data are as is.

Results: In the enco + bini arm, the 5-year OS rate (95% CI) in all pts (n=192), those with lactate dehydrogenase (LDH) $\leq$ upper limit of normal (ULN) at baseline (n=137), and low tumor burden (n=88) was 35% (28–42), 45% (36–53), and 48% (37–58), respectively (data cut-off: Sep 15, 2020). Other efficacy results are shown in the table. Safety results were consistent with the known tolerability profile of enco + bini. Adverse events (AEs) occurring in $\geq$ 20% of enco + bini pts were nausea, diarrhea, vomiting, arthralgia, fatigue, increased blood creatinine phosphokinase (CPK), headaches, constipation, asthenia, and pyrexia. Grade 3/4 AEs occurring in $\geq$ 2.5% of pts in the enco + bini were hypertension, pyrexia, abdominal pain, diarrhea, and vomiting. Grade 3/4 abnormal laboratory values occurring in $\geq$ 2.5% pts in the enco + bini arm were increased gamma-glutamyl transferase, increased blood CPK, anemia, increased alanine transaminase, and hyperglycemia. 12%–14% of pts in each arm discontinued tx due to AEs. The most common anti-cancer tx after enco + bini were checkpoint inhibitors. Additional analyses will be presented.

Table: 1041MO

	Enco + bini (n=192)	Enco (n=194)	Vem (n=191)
5-year PFS rate*	23 (16–30)	19 (13–27)	10 (5–18)
5-year OS rate*	35 (28–42)	35 (28–42)	21 (16–28)
LDH $\leq$ ULN n LDH > ULN n Low tumor burden n	45 (36–53) 137 9 (3–18) 55 48 (37–58) 88	42 (33–50) 147 14 (6–26) 47 50 (39–60) 94	28 (21–36) 139 4 (1–12) 52 38 (28–49) 84
Objective response rate*	64 (57–71)	52 (44–59)	41 (34–48)
Disease control rate*	92 (87–96)	84 (78–89)	81 (75–86)
Complete response†	27 (14)	15 (8)	16 (8)
Partial response†	96 (50)	85 (44)	62 (32)
Stable disease† (includes non-complete response or non-progressive disease)	54 (28)	63 (32)	77 (40)
Progressive disease† (includes best response of unknown or no assessment)	15 (8)	31 (16)	36 (19)

*% (95% CI) †n (%)

Conclusions: Updated results with enco + bini indicate continued long-term benefit in pts with advanced/metastatic *BRAF*^{V600} melanoma.

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1042P Anti-PD1 (PD1) monotherapy or in combination with ipilimumab (IPI) after BRAF/MEK inhibitors (BRAF/MEKi) in BRAF mutant metastatic melanoma (MM) patients (pts)

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Background: Pts with *V600*BRAF mutant MM have numerically higher rates of progression-free survival (PFS) and overall survival (OS) with 1st line IPI+PD1 vs PD1. Whether this is also true after BRAF/MEKi therapy is yet to be determined. We aimed to: (1) determine the efficacy and safety of PD1 vs IPI+PD1 after BRAF/MEKi; and (2) identify the subgroup of pts with >3 yrs OS with PD1+/-IPI after BRAF/MEKi.

Methods: MM pts treated with BRAF/MEKi who had subsequent PD1 or IPI+PD1 at 8 melanoma centres were included. The endpoints were objective response rate (ORR), PFS, OS & safety for PD1 vs IPI+PD1. Multivariate analysis (MVA) and backward elimination technique were used to build models to predict those pts with OS > 3 yrs with PD1+/-IPI after BRAF/MEKi.

Results: Of 200 MM pts treated with BRAF/MEKi, 115 (57%) had subsequent PD1 and 85 (43%) had IPI+PD1. Differences in baseline characteristics for PD1 vs IPI+PD1 included med. age (63 vs 54 yrs), ECOG PS >= 1 (62% vs 44%), time between BRAF/MEKi and PD1+/-IPI (0.5 vs 0.1 mo), M1C/M1D stage (72% vs 94%) and brain metastases (mets) (38% vs 65%). Med. follow-up from start of IPI+/-PD1 was 37.8 mo (CI 95% 33.9 – 52.9). ORR was 36%; 34% with PD1 vs 39% with IPI+PD1 (p>0.05). PFS rate at 1 yr was 34%; 33% with PD1 vs 34% with IPI+PD1 (med PFS 3.8 vs 4.2 mo, p>0.05). OS rate at 1 yr was 55%; 53% with PD1 vs 58% with IPI+PD1 (med OS 14.4 vs 20.5 mo, p>0.05). >=G3 toxicity was higher with IPI+PD1 (31%) vs PD1 (8%) (p<0.05). On MVA, ECOG PS=0 & >=G3 toxicity were associated with higher ORR. ECOG PS=0, elective BRAF/MEKi cessation & absence of liver metastases were associated with longer PFS and OS. OS was significantly longer with IPI+PD1 vs PD1 in non-V600E mutations (80% vs 51%), but no difference in V600E mutations (53% vs 53%). PFS and OS were numerically longer with IPI+PD1 vs PD1 across all other subgroups except for OS in females & III/M1A/M1B stages. 22% of pts had OS >3 yrs with PD1+/-IPI after BRAF/MEKi; the combination of ECOG PS=0, absence of liver metastases and normal LDH identify these pts (AUC=0.82).

Conclusions: IPI+PD1 appears superior to PD1 after BRAF/MEKi in most subgroups of pts, although is more toxic. A combination of clinical factors can accurately identify pts with >3 yrs OS with PD1+/-IPI after BRAF/MEKi.

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1043P NF1 mutations and immune checkpoint inhibitor outcomes in patients with BRAF wildtype melanoma

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Background: Three genomic subtypes of BRAF wildtype (WT) cutaneous melanoma (CM) include NRAS mutant (mut), NF1 mut, triple wildtype (tWT). NF1 mut melanoma have a high tumor mutation burden and have been associated with increased responsiveness to immune checkpoint inhibitors (ICI) in some retrospective studies. We evaluated whether the NF1 subtype was associated with improved ICI outcomes in our population.

Methods: This is a single center retrospective cohort study including patients (pts) with BRAF V600 WT unresectable/ metastatic melanoma, who received anti-PD1 +/- anti-CTLA4 between 2012-2021. Next Generation Sequencing (NGS) was performed in tumor samples for NF1 and NRAS mut. Mucosal, uveal or acral-lentiginous melanomas were excluded. ICI treatment response was determined by investigator assessment of clinical and radiologic parameters. X^2, Fisher's exact and U-Mann Whitney tests were used to compare groups. Log-rank tests and Kaplan Meier curves were used to assess clinical progression free survival (cPFS) and overall survival (OS).

Results: Our cohort included 68 pts, 43 (64.2%) were male and median age was 68 (30 to 93). Combination ICI was given to 31 (45.6%) and anti-PD1 monotherapy to 37 (54.4%) pts. Median follow-up was 10.6 months. NGS revealed 17 (25%) NF1-only pathogenic variants, 28 (41.2%) NRAS mut and 3 (4.4%) NF1/NRAS co-mutation (4.4%). There were no significant differences in gender, age, LDH, M stage or ICI regimen between NF1-only mut versus NRAS mut and tWT pts. Treatment responses were seen in 82.4% (14/17) NF1 mut pts and in 49% (25/51) NRAS/tWT pts treated with ICI ($p=0.016$). NF1 mut pts had longer median cPFS (not reached, >21 months) compared to NRAS/tWT pts (15.2 months) ($p=0.040$). Median OS was not reached in either group, but there was a trend toward longer median OS in NF1 mut pts versus NRAS/tWT pts (HR: 0.373 95%CI 0.11-1.26 $p=0.113$).

Conclusions: Our data provide external validation to independent observations that NF1 mut are associated with improved ICI outcomes in pts with BRAF V600 WT metastatic cutaneous melanoma. Prospective validation of NF1 mut as complementary biomarker of responsiveness is warranted.

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1044P Sequential targeted and immunotherapies in stage IV melanoma

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Background: Targeted (TT) and immunotherapies (IT) significantly improved the outcome of stage IV melanoma patients (pts). However, data on the optimal therapy sequence are missing for patients with BRAFV600 mutated melanoma.

Methods: In this retrospective study, we analyze stage IV melanoma patients who were treated at the Center for Dermato-Oncology of the Tuebingen University between January 2011 and December 2018. Patients received IT 1stline (1L) and 2nd line (2L) (IT-IT); IT 1L and TT 2L (IT-TT); TT 1L and IT 2L (TT-IT) and TT 1L and 2L (TT-TT). The date of data cut-off analysis was October 2020. Follow-up time (FUP) was the time between stage IV diagnosis and death or last contact. We performed descriptive analyses of pts characteristics for the subgroups mentioned and overall survival (OS) analysis. Data on best overall response, progression-free survival, and other subgroup analyses will also be presented.

Results: We included 1046 stage IV melanoma pts with a median FUP of 29 months (M) [IQR: 14M:67M]. 396 patients of the entire cohort (n=1046) have received at least two lines of systemic therapy. The number of pts treated with each therapy sequence is as follows: IT-IT 91 pts, TT-IT 83 pts, IT-TT 41 pts, and TT-TT 33 pts; 148 pts received other combinations of 1L and 2L. When comparing the subgroup of patients with BRAFV600 mutated melanoma who received sequential therapy with IT-TT or TT-IT (Pearson's chi-squared test) there were no statistically significant differences regarding sex, age, presence of elevated LDH, or elevated protein S100 at the time of stage IV diagnosis. The median OS (mOS) and the 5-years (5-y) OS rate for the whole collective (n=1046) was 19M and 29%, respectively. For pts receiving at least two lines of systemic therapy (n=396), the mOS and 5y OS rate were 21M and 25%, respectively. For the 4 therapy sequences, the mOS and 5y OS rate were: IT-IT 36M and 34%; TT-IT 18M and 16%; IT-TT 17M and 32%; TT-TT 32M and 31%, respectively. There was no statistically significant difference in mOS between the 4 sequences (p=0.084) or the IT-TT and TT-IT sequences (p=0.677).

Conclusions: 2L therapies seem to have a modest impact on OS. There was no significant difference in terms of OS between the four sequences.

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1045P Comparison between first-line target therapy and immunotherapy in different prognostic categories of BRAF mutant metastatic melanoma patients

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Background: BRAF and MEK inhibitors target therapies (TT) and AntiPD1 immunotherapies (IT) are available first-line treatments for BRAF v600 mutant metastatic melanoma patients (pts). ECOG PS (E), baseline LDH (L), baseline number of metastatic sites (N)are well known clinical prognostic markers that identify different prognostic categories of pts. Direct comparison between first-line TT and IT in different prognostic categories could help in first-line treatment decision.

Methods: This is a retrospective analysis conducted in 14 Italian centers. We analyzed data about 454 metastatic melanoma pts (without brain metastasis), Pts were divided in three different prognostic risk categories: group A: pts with E=0, L within normal range, and N less than 3; group B: pts not included in group A or C; group C: pts with E>0, L over the normal range, and N more than 3. For each prognostic group we compared TT and IT in terms of PFS, OS, DCR.

Results: In the table we report the comparison between TT and IT in groups A, B, C, in terms of PFS, OS, DCR.

Table: 1045P

	Group A (better prognosis)		Group B (intermediate prognosis)		Group C (worse prognosis)	
	TT	IT	TT	IT	TT	IT
N° patients	140	36	196	38	41	3
mPFS (months)	36	12	11,5	5	6,4	1,8
HR (95%IC) p value	1,949 (1,180-3,217) 0,009		1,535 (1,036-2,275) 0.033		4,860 (1,399-16) 0,013	
PFS at 1y (%)	70	48	40	29	18	nr
PFS at 2y (%)	57	43	30	23	nr	nr
PFS at 3y (%)	48	37	22	23	nr	nr
PFS at 5y (%)	43	nr	12	23	nr	nr
mOS (months)	Not	55	19	20,5	9	5,5
HR (95%IC) p value	Reached 1,195 (0,602-2,373) 0,610		0,886 (0,546-1,437) 0,623		3,443 (0,991-11,9) 0,052	
OS at 1y (%)	88	80	64	75	28	nr
OS at 2y (%)	80	77	48	48	10	nr
OS at 3y (%)	65	63	36	37	5	nr
OS at 5y (%)	55	43	27	30	nr	nr
Disease control rate (CR+PR+SD) (%) P value	99% <0.001	75%	85% <0.001	47%	66% 0.258	33%

Conclusions: In good prognosis group A (baseline ECOG PS 0, LDH within normal range, <3 metastatic sites) TT showed statistically significant better PFS than IT, also in a long term period, suggesting that TT can be a good first-line option for this pts category. Only in Group B we observed a crossing of the survival curves after the 3rd year of observation in favor of IT. Few pts were enrolled in group C, so few conclusion can be made about it, even if TT showed grater efficacy. DCR was better for TT in all groups.

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1046P First-line anti-PD-1 antibody monotherapy versus anti-PD-1 plus anti-CTLA-4 combination therapy in Japanese mucosal melanoma: A retrospective, multicenter study (JMAC study)

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Background: Anti-PD-1 antibody monotherapy (PD1) leads to favorable responses in advanced cutaneous melanoma (CM) among Caucasian populations; however, recent studies have indicated limited efficacy in mucosal melanoma (MM) than in CM. Thus, advanced MM patients (pts) are candidates for anti-PD-1 plus anti-CTLA-4 combination therapy (PD1+CTLA4). Meanwhile, data on the efficacy of immunotherapy in MM are limited. We aimed to compare the efficacies of first-line PD1 and PD1+CTLA4 in Japanese advanced MM pts in the real-world setting.

Methods: Advanced MM pts who received PD1 or PD1+CTLA4 were included from 24 Japanese institutions. Clinical responses were assessed using the RECIST criteria. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier analysis. Toxicity was assessed according to CTCAE 5.0.

Results: Altogether, 329 pts with advanced MM (head and neck 184; urogenital organs 76; gastrointestinal tract, 69) were included in the study. PD1 and PD1+CTLA4 were used in 263 and 66 pts, respectively. Baseline characteristics such as ECOG performance status, TNM stage, LDH level, and the number of metastatic organ sites were comparable between the PD1 and PD1+CTLA4 groups, except for age (median age 71 vs. 65; $P < 0.001$). No significant differences in objective response rate were observed between the PD1 and PD1+CTLA4 groups (26% vs. 29%; $P = 0.26$) or PFS and OS (median PFS 5.9 months vs. 6.8 months; $P = 0.55$, median OS 20.4 months vs. 20.1 months; $P = 0.54$). Multivariate survival analysis using Cox proportional hazards model revealed that PD1+CTLA4 did not prolong PFS and OS (PFS: hazard ratio (HR) 0.83, 95% confidential interval (CI) 0.58−1.19, $P = 0.30$; OS: HR 0.89, 95% CI 0.57−1.38, $P = 0.59$), although ECOG performance status 0, normal LDH level, and a small number of metastatic sites impacted PFS and OS. Due to immune-related adverse events, the treatment cessation rate was higher in the PD1+CTLA4 group than in the PD1 group (55% vs. 17%).

Conclusions: First-line PD1+CTLA4 did not present better clinical efficacy than PD1 in Japanese MM pts, despite the higher rate of immune-related adverse events.

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1047P Efficacy of checkpoint inhibitors (CPIs) in acral melanoma (AM)

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Background: AM is a rare melanoma subtype with poor prognosis. While retrospective data suggests low activity of PD1 alone, no data are available on the efficacy of combination PD1/CTLA4 in AM. AM primary site is associated with differences in tumour mutation burden, which may impact CPI activity. We examined the efficacy of CPIs in AM, and in primary site subgroups.

Methods: Patients (pts) with unresectable stage III/IV AM treated with at least one line of CPI (PD1 and/or ipilimumab (Ipi) were studied. Disease/patient characteristics and therapy were examined. Multivariable logistic and Cox regression analysis were conducted. Primary outcomes were objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Results: 369 pts were included; median age at first diagnosis was 63yrs (20-88), 80% Caucasian, 53% male, 12% BRAF, 13% NRAS, 7% KIT mutant; 41 had received prior adjuvant CPI. Median time from primary diagnosis to development of advanced disease was 19.6 months [1.8-260.6]. Primary site of AM was 260 (70%) plantar, 25 (7%) palmar and 84 (23%) subungual. Excluding 41 pts who received adjuvant CPI, 1st line systemic therapy included 151 (46%) PD1, 51 (15%) Ipi, 54 (16%) combination CPI and 72 (22%) other therapies (e.g. chemotherapy, targeted therapy). At commencement of 1st-line therapy, 30% were stage M1c, 53% ECOG 0 and 19% had elevated LDH. Median follow up was 8.1yrs (7.68-10.66). ORR was highest with combination CPI; this remained significant in multivariate analysis (Table). PFS was significantly associated with 1st-line therapy, however PFS was not significantly different between PD1 and combination CPI (p=0.42) (Table). Median OS was 2.3yrs (95% CI 1.9-2.6) and did not vary by 1st-line therapy received (p=0.57). No outcome differences were found between primary sites.

Table: 1047P

OR = Odds ratio HR = Hazard ratio	PD1 (N=151)	CTLA4 (N=51)	PD1+CTLA4 (N=54)
ORR	26%	12%	44%
Univariable OR	1	0.43 (95%CI, 0.19-0.97), p=0.0009	2.24 (95%CI, 1.24-4.07), p=0.0023
Multivariable OR	1	0.45 (95%CI, 0.20-1.03), p=0.0015	2.38 (95%CI, 1.30-4.36), p=0.0015
PFS (months)	7.0 (95%CI, 5.3-1.5)	4.9 (95%CI, 4.1-6.2)	7.3 (95%CI, 4.9-13.2)
Univariable HR	1	1.57 (95%CI, 1.15-2.14), p=0.0042	0.91 (95%CI, 0.66-2.14), p=0.56
Multivariable HR	1	1.64 (95%CI, 1.20-2.24), p=0.0019	0.87 (95%CI, 0.63-1.21), p=0.42

Conclusions: CPIs are active in pts with advanced AM, with superiority of combination CPI over PD1 alone in terms of ORR but not PFS or OS. Primary AM site did not impact CPI efficacy.

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1048P Baseline and post-treatment biomarkers of resistance to anti-PD-1 (aPD1) therapy in acral and mucosal melanoma

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Background: Acral and mucosal melanoma patients may have lower response to aPD1 therapy, providing a unique opportunity to characterize resistance mechanisms.

Methods: This observational study identified 3 groups of acral/mucosal melanoma patients treated by aPD1 monotherapy at a Korean tertiary care hospital: 1) Primary resistance (n=61), 2) Secondary resistance (n=49), 3) Non-progressors (n=14). Pre-treatment and paired pre- and post-treatment biopsies were assayed for PD-L1 IHC, tumor mutational burden (TMB), 18-gene T cell-inflamed gene expression profile ($Tcell_{inf}$GEP) and other key tumor biology and microenvironment mRNA signatures, and immune cell infiltration (CD8+, FOXP3+, CD11c+) by IHC. Descriptive statistics were used to compare non-progressors to resistant patients in baseline samples. Patient-matched paired analysis compared pre-post samples from patients with primary and secondary resistance, adjusting for baseline measurements and $Tcell_{inf}$GEP (GEP) for mRNA signatures.

Results: At baseline, the proportion of PD-L1-positive, TMB-high patients, and median values of GEP, CD8+, FoxP3+, CD11c+ were higher in non-progressors compared to resistant patients overall. At baseline, primary resistant patients had lower values of PD-L1 and GEP compared to secondary resistance, while TMB, CD8, FOXP3, CD11c did not differ. Among resistant patients overall, PD-L1 and GEP increased pre- to post-treatment, while WNT and INFα mRNA signatures decreased. After adjusting for baseline, suggestive differences in changes from pre- to post-treatment values were observed comparing secondary resistance and primary resistance; the change from baseline was lower for gMDSC, and higher for FOXP3+, CD11C+ in secondary compared to primary resistance.

Conclusions: Limitations for this exploratory study include, a relatively small sample size, post-treatment samples unavailable for non-progressors, and variation in post-treatment sample collection time. However, the unique availability of baseline and post-treatment biomarkers provides evidence for potential differences comparing non-progressors and resistant patients as well as for primary and secondary resistance.

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1049P Clinical models to predict response in mucosal melanoma (MM) patients (pts) treated with anti-PD-1 (PD1) or combined with ipilimumab (PD1+IPI)

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Background: MM is a rare subtype of melanoma with distinct biology. Data on the efficacy of immunotherapy in MM is limited. We aimed to determine the immunotherapy efficacy by primary site (prim) and race.

Methods: Baseline characteristics of MM treated with PD1+/-IPI from 24 cancer centers were collected. Primary endpoints were response rate (RR), progression-free survival (PFS), overall survival (OS) by prim (naso-oral, urogenital, anorectal, other), race (Caucasian, Asian, Other) and treatment (PD1 v PD1+IPI). Univariate and multivariate Cox proportional hazard model analyses were conducted.

Results: 518 pts were included; med age 64 yrs (range 25-93); 326 (63%) Caucasian, 154 (30%) Asian & 38 (7%) Other; 113 (22%) anorectal prim, 170 (33%) urogenital, 194 (38%) naso-oral & 41 (8%) other; 150 (29%) LDH >ULN at baseline; 328 (63%) received PD1 & 190 (37%) PD1+IPI; med f/u 34 months (17-50). Baseline characteristics were similar between PD1 v PD1+IPI, except Stage IV (79% v 70%, p=0.02). PD1+IPI was more frequent in Caucasians than Asians (40% v 14%, p<.001) RR did not differ by prim, race & treatment (Table). RR for naso-oral was numerically higher for PD1+IPI v PD1 for Caucasians (36% v 28%) & Asians (57% v 25%). Factors prognostic of short PFS were Stage IV (p=0.02), ≥2 organ metastases (mets) (p=0.01), ECOG PS ≥1 (p=0.01) & presence of liver (p=0.01), lung (p<0.01) & bone (p<0.01) mets. Factors prognostic of short OS were advanced Stage III/IV (p=0.04), ≥2 organ mets (p<0.01), ECOG PS ≥1 (p=0.01) & presence of liver (p=0.01), lung (p<0.01), bone (p<0.01) & pancreatic (p=0.01) mets.

Table: 1049P

		Race		Treatment		Overall
		Caucasian	Asian	PD1	PD1+IPI	
Overall RR		99/326 (30%)	37/154 (24%)	91/328 (28%)	59/190 (31%)	150/518 (29%)
RR site	Anorectal	26/80 (33%)	5/24 (21%)	20/68 (29%)	16/45 (36%)	36/113 (32%)
	Urogenital	33/121 (27%)	8/37 (22%)	31/99 (31%)	15/71 (21%)	46/170 (27%)
	Naso-oral	36/123 (29%)	19/66 (29%)	35/130 (27%)	24/64 (38%)	59/194 (30%)
RR race	PD1	57/189 (30%)	29/128 (23%)	-	-	-
	PD1+IPI	42/137 (31%)	8/26 (31%)	-	-	-
PFS	mPFS mo (med, 95% CI)	5 (4-6)	4 (3-6)	5 (4-6)	4 (3-6)	4 (4-6)
	3 yr PFS (95% CI)	16% (12-21)	17% (12-26)	16% (13-22)	16% (10-25)	16% (13-21)
OS	mOS mo (med, 95% CI)	21 (18-26)	18 (14-25)	18 (16-23)	21 (19-27)	19 (18-24)
	3 yr OS (95% CI)	33% (27-40)	30% (22-42)	32% (27-39)	29% (21-40)	32% (27-37)

*Other site not shown

Conclusions: Pts with MM have poor prognosis. Efficacy of PD1+/-IPI is similar for site of prim & race. In Caucasians & Asians naso-oral was the most common prim site & showed numerically higher response to PD1+IPI. At other sites, addition of IPI does not appear to give greater benefit over PD1. Other clinical factors were predictive and prognostic for treatment outcome.

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1050P Outcome and impact of immune related adverse events in patients with advanced melanoma treated with checkpoint inhibitors

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Background: The impact of immune related adverse events (irAEs) on melanoma outcomes is unclear. We evaluated the survival of patients (pts) with locally advanced (LA)/metastatic melanoma (MM) treated with immune checkpoint inhibitors (ICI), as well as risk factors for and impact of irAEs.

Methods: Pts ≥18 years (y) with LA/MM who received ≥1 cycle of an ICI at BC Cancer from 2012-2019 were identified using the BC Cancer Registry and Pharmacy databases. IrAEs were graded using the CTCAEv5. A landmark analysis of pts progression-free at 20 weeks was performed.

Results: 451 pts were identified: cutaneous (n=329, 73% [BRAF+ = 42%]), mucosal (n=30, 7%), ocular (n=41, 9%), and unknown (n=51, 11% [BRAF+ = 33%]) subtypes. With a median follow-up of 30 months (m), 2-y overall survival (OS) was 47%, 31%, 29%, and 60% per subtype, respectively ($p<0.001$). Combination ipilimumab/nivolumab (ipi/nivo), PD1 inhibitor alone (PD1), and ipilimumab alone (ipi) were given to 96 (21%), 275 (61%) and 80 (18%) pts, respectively. 2-y OS was superior for ipi/nivo vs PD1 (63% vs 49%, $p=0.01$), and remained significant when stratified by cutaneous/unknown (62% vs 53%, $p=0.05$) and mucosal (73% vs 21%, $p=0.025$). However, this difference was only observed in males (2-y OS 69% vs 47%, $p=0.001$; females, $p=0.9$). 62% of pts had ≥1 irAE: endocrine (21%), GI (20%), and skin (34%). Grade (gr) ≥3 irAEs by treatment were 46% (ipi/nivo) vs 11% (PD1) vs 15% (ipi), ($p<0.001$). Vitiligo (12%) was associated with improved OS (2-y OS 84% vs 41%, $p<0.001$). In a landmark 20-week analysis, OS was similar by irAE development ($p=0.91$). Gr ≥2 irAE was associated with normal LDH (82% vs 19%, $p=0.01$) and sex (male 69% vs female 31%, $p=0.019$) in ipi/nivo, but no risk factors were identified in PD1. Steroid use ≤2m before PD1 reduced irAE risk but also OS ($p<0.0001$) (including M1d, 2-y OS 57% vs 26%, $p=0.016$), an impact not observed with ipi/nivo ($p=0.927$).

Conclusions: Males have a higher risk of gr ≥2 irAEs and improved OS using ipi/nivo. Steroid use before ICI was associated with reduced toxicity and efficacy of PD1 inhibitor therapy, but not in those treated with ipi/nivo. Further studies that correlate biomarkers with irAE risk and outcome across ICI therapies are needed.

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1051P Impacts of skeletal muscle on survival in resected stage III malignant melanoma

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Background: Sarcopenia (low skeletal muscle index, SMI) and myosteatosis (low skeletal muscle density, SMD) have been associated with worse survival in various cancers. This study's objectives were to assess impacts of body composition on survival in patients with resected stage III melanoma.

Methods: A retrospective review was performed of resected stage III melanoma patients in Alberta, Canada from 2007-2017. Pre-operative CT scans were analyzed at L3 to determine SMI and SMD. Cohort-specific SMI and SMD cut-offs that optimally predicted overall survival (OS) were identified through stratification, in addition to testing cut-offs previously established in the literature. OS, melanoma-specific survival (MSS), and recurrence-free survival (RFS) were determined from date of surgery and analysed using Cox regressions. Age, sex, stage subgroup, ECOG PS, and tumor location were included in multivariate analyses.

Results: 330 patients were included in the final analysis. Mean age was 56 years, 62.4% of patients were male, and 97% had a baseline ECOG status of 0-1. At time of censoring 150 patients (45.6%) had died, with 110 deaths (73.3%) attributable to melanoma recurrence. Based on literature cut-offs, 46.7% had sarcopenia and 46.4% had myosteatosis. Both sarcopenia (HR 1.50, 95% CI 1.08-2.09, $p=0.016$) and myosteatosis (HR 1.57, 95% CI 1.10-2.24, $p=0.013$) were associated with decreased OS in multivariate analysis. Based on cohort-specific cut-offs, sarcopenia prevalence was 20% and myosteatosis prevalence was 18.2%. Sarcopenic patients defined by cohort-specific cut-offs had decreased OS (HR 2.38, 95% CI 1.64-3.45, $p<0.001$) and MSS (HR 1.85, 95% CI 1.16-2.95, $p=0.009$) in multivariate analysis. Myosteatosis defined by cohort-specific cut-offs predicted worse OS (HR 2.30, 95% CI 1.56-3.37, $p<0.001$), MSS (HR 2.33, 95% CI 1.48-3.69, $p<0.001$) and RFS (HR 1.50, 95% CI 1.03-2.19, $p=0.035$) in a multivariate model.

Conclusions: Sarcopenia and myosteatosis are prevalent in stage III melanoma. Both factors, defined using two sets of cut-offs, are associated with decreased OS. In addition, sarcopenia and myosteatosis defined using cohort-specific cut-offs predicted decreased MSS.

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1052P Survival outcomes predicted by irAEs on 18F-FDG-PET in response to PD-1 antibody therapy in metastatic melanoma

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Background: PD-1 antibody therapy has revolutionised the landscape of metastatic melanoma treatments and outcomes. The aim of our study is to investigate whether immune related adverse events (irAEs) or granulomatous/reactive nodal changes visible on 18F-FDG-PET during treatment with PD-1 antibody therapy for metastatic melanoma predicts improved overall survival.

Methods: Patient demographics, treatment regimes, toxicity profiles and 18F-FDG-PET scans were collected for patients who underwent treatment at Alfred Health in Melbourne, Victoria between 2015 and 2019 for advanced melanoma. Data were extracted from each patient's electronic medical record. Patients were included if they were treated with 1st line PD-1 antibody +/- CTLA-4 antibody therapy for unresectable stage III or stage IV metastatic cutaneous melanoma. Patients were excluded if an 18F-FDG-PET was not performed both during and prior to commencement of immunotherapy. Two blinded-nuclear medicine physicians reviewed 18F-FDG-PET imaging at baseline and following immunotherapy. The review criteria included granulomatous/reactive changes and PET detected irAEs. Clinically reported irAE were also collected. Statistical analysis was performed using IBM SPSS software.

Results: A total of 103 patients (68% male) met the inclusion criteria for the study. The largest proportion of individuals had M1c disease (26.2%) followed by unresectable stage III (25.2%), M1b (21.4%), M1a (16.5%) and M1d (10.7%) respectively. Most individuals received single agent anti-PD-1 (71.6%) whereas a smaller proportion received combination therapy with CTLA4 antibody therapy (28.4%). The median follow up period was 3.6 years. Patients with irAEs visible on 18F-FDG-PET during treatment had improved survival ($p=0.004$), this remained significant after adjusting for age, gender, stage and baseline LDH ($p=0.03$). Granulomatous or reactive nodal changes visible on 18F-FDG-PET did not have any significant impact on survival outcomes ($p=0.74$) nor did clinically reported irAEs ($p=0.60$).

Conclusions: This study demonstrates that irAEs visible on ^{18}F-FDG-PET during PD-1 antibody therapy for metastatic melanoma predicts improved overall survival.

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1053P Tumour mutational burden (TMB) assessment using next generation sequencing (NGS) for the prediction of complete response (CR) to immunotherapy (IO) in metastatic melanoma

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Background: TMB is an emerging biomarker of IO response, however in the setting of a wide variation in median TMB values between cancer subtypes, histology specific thresholds predicting response remain unclear. The TruSight Oncology 500® (TSO 500) is a comprehensive 523 gene NGS assay and is highly concordant with whole exome sequencing in TMB assessment. Thresholds predicting meaningful response to IO such as CR in metastatic melanoma using this panel are needed.

Methods: Consenting cutaneous melanoma patients treated with IO with radiographic or metabolic CR of at least 6 months duration, and patients with early progression (EP) (confirmed disease progression within 6 months, including stage III patients on adjuvant IO) had IO-naïve tissue sequenced with the TSO 500. TMB values in mutations per megabase (mut/Mb) were calculated and compared with the Mann–Whitney U test. TMB thresholds predicting CR vs EP were assessed using area under the receiver operator curve (AUC) regression analysis, after adjustment for covariates including age, stage, *BRAF* status & IO type.

Results: 18 EP samples and 34 CR tumours have been sequenced with adequate quality control. 31/34 CRs are ongoing. 50% of EP and 56% of CR patients had received anti-PD1 monotherapy with remainder having received combination therapy. TMB correlated strongly with CR ($p<0.001$) with a median TMB of 13.3 (EP) vs 53.2 (CR). The AUC for TMB by responder group (95%CI) was 0.843 (0.724-0.962) ($p<0.001$). Thresholds predicting CR vs EP are shown in the table. TMB as a continuous variable correlated strongly with CR (OR of 1.03 for every 1 mut/Mb TMB increase), both in univariate and multivariate modelling ($p=0.014$).

Table: 1053P TMB thresholds predicting CR after IO based on AUC regression

TMB threshold	Sensitivity (%)	Specificity (%)	OR (95% CI)
TMB>10*	100	44.4	Not calculable
TMB>16	91.2	61.1	16.24 (3.56-74.05) P<0.001
TMB>23**	76.5	77.8	11.38 (2.91-44.53) p<0.001

*Maximum sensitivity cutoff, **Optimal sensitivity & specificity cutoff using Youden Index

Conclusions: Overall, TMB measured using the TSO 500 is a strong predictor of CR. Ongoing validation in a cohort of 40 patients will be presented.

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1054P FDG-PET to predict long-term outcome from anti-PD1 (PD1) therapy in metastatic melanoma

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Background: We have shown that 75% of patients (pts) with metastatic melanoma treated with PD1 who have not progressed by 1-year on RECIST or clinical grounds have complete metabolic response (CMR) on PET imaging, including two-thirds of pts with partial response (PR) on CT. CMR pts have excellent medium-term survival, with progression seldom seen in 2 years. We now report 5-year outcomes.

Methods: Retrospective analysis of 104 pts with baseline and 1-year PET and CT. 1-year response was determined using RECIST for CT and EORTC criteria for PET, coded as CMR, PMR, stable disease (SMD) or progressive disease (PMD). Progression-free survival (PFS) and overall survival (OS) were determined from 1-year landmark.

Results: At median follow-up of 61 months (range 58-64) from 1-year PET, 94.2% of pts remained alive and all but one had discontinued treatment after a median of 23 months (range 1-59). Disease progression occurred in 19 pts (18%), compared to 14 (13%) at 24 months; 7 (37%) with CMR, 10 (53%) while on PD1 and 12 (63%) in solitary sites for which 8 (67%) received local treatment. RECIST PFS 5-years after PET was superior in pts with CR compared to PR/SD, CMR compared to non-CMR, and in pts with PR on CT, PFS was superior in PR + CMR compared to PR + non-CMR (Table). 34 (33%) pts (13 in CR, 30 CMR) discontinued treatment within 12 months either electively or due to toxicity with no impact on PFS compared to those that discontinued beyond 12 months (p=0.41). Despite progression events, OS at 5-years was excellent and similar in pts with CR & PR/SD, CMR & non-CMR, and within those with PR by PET response.

Conclusions: 5-years after PET imaging, sustained responses are observed in the vast majority of pts with CMR on PET and PET continues to predict outcome better than CT. In the minority of patients that progress, often in solitary sites and managed locally, OS remains excellent. PET is effective in evaluating residual lesions on CT and has an important role in predicting long-term benefit and potential early treatment cessation.

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1055P Prognostic relevance of tumor-infiltrating lymphocytes in early-stage melanoma

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Background: The use of immune checkpoint therapies is being investigated in early-stage melanoma patients (pts). So far there is no definitive prognostic and/or predictive biomarker. The presence of tumor-infiltrating lymphocytes (TILs) has been associated with a better prognosis in several malignancies, including melanoma. Using a digital pathology approach, we intended to identify a cut-off based on the percentage of TILs (%TILs) as a prognostic factor in this setting.

Methods: We analyzed 655 H&E stainings of primary melanomas of pts diagnosed with stage I/II melanoma between January 2000 and December 2018 in the Center for Dermato-Oncology at the University of Tuebingen. We used the software QuPathv1.2 to perform semi-automated determination of %TILs and the R package Evaluate Cutpoints to identify the best cut-off for stratification. Our primary endpoint was relapse-free survival (RFS) defined as the time from the initial diagnosis to first local or distant metastasis.

Results: We identified 381 pts in stage I and 274 in stage II (n=655). The median follow-up time was 70 months [IQR 39-112]. The optimized TIL% cut-off of 11.37 defined two groups: low and high %TILs, respectively below and above 11.37. The 10-years RFS rate was 53% and 75% for the low and high %TILs groups, respectively (95% CI: 40-66 and 71-79). There was a statistically significant difference for RFS in the univariate (UV) Cox analysis between the two groups ($p<0.0001$; HR: 2.51 (95%CI: 1.67-3.78), favoring pts with high %TILs). This RFS difference was also statistically significant in the UV Cox analysis in stage II alone ($p<0.0001$; HR:2.45; 95%CI: 1.55-3.88), but not in stage I. In the multivariate Cox analysis including tumor thickness (pT), ulceration and %TILs, pT and ulceration remained significant, with a trend for significance in %TILs, ($p<0.0001$; HR: 1.26 (95%CI: 1.19-1.34); $p=0.003$; HR: 1.77; (95%CI: 1.22-2.58) and $p=0.148$; HR: 1.39 (95%CI: 0.89-2.18), respectively).

Conclusions: Stage I/II melanoma pts with high %TILs had a statistically significant improved RFS compared to pts with low %TILs. %TILs is an easily determinable and semi-automated parameter that could be used to identify pts who would benefit from adjuvant treatment or a more personalized follow-up.

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Table: 1054P

	Response category at 1 year	2-year			5-year		
		2-year survival (%)*	2-year HR *(95% CI)*	2-year *p*-value	5-year survival (%)*	5-year *HR (95% CI)*	5-year *p*-value
PFS	CR	100	0.18 (0.06-0.56)	0.06	93	0.27 (0.06-1.15)	0.06
	PR/SD	79			76		
	CMR	95	0.06 (0.02-0.23)	<0.06	90	0.13 (0.05-0.33)	<0.01
	Non-CMR	54			54		
	PR + CMR	93	0.07 (0.02-0.27)	<0.01	88	0.18 (0.06-0.55)	<0.01
	PR + non-CMR	48			59		
OS	CR	-	-	-	100	-	0.12
	PR/SD	-			95		
	CMR	-	-	-	97	-	0.14
	Non-CMR	-			94		
	PR + CMR	-	-	-	96	-	0.64
	PR + non-CMR	-			95		

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1056P Survival of patients with advanced melanoma according to first-line treatment and key prognostic factors: Real-world data from GEM1801 study

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Background: Targeted therapy (TT) and immune-check-point inhibitors (CPi) have improved the survival of patients (pts) with advanced melanoma (mel). Real-world data of these treatments are needed to confirm the results of clinical trials.

Methods: GEM1801 is a prospective observational study including 400 pts with resected stage III and advanced mel diagnosed since 2018 in Spain. Objectives were to analyze the clinical and pathological presentation, treatment choice and health outcomes. We report results of the advanced mel group (N=357).

Results: Median age was 65 years, ECOG 0-1 85.7% and AJCC 8th Ed stage IV 90.7% (24.9% a, 14.3% b, 34.7% c and 16.9% d). *BRAF,* reported in 348 pts (97.5%), was *BRAF*^{V600}-mutated (Mut) in 50.4%. LDH, reported in 302 pts (84.6%), was > upper limit normal (ULN) in 32.8%. First-line (1L) was CPi in 94.9% of *BRAF*-wild-type (wt) and 30% of *BRAF* ^{V600}-Mut. For TT, BRAF+MEK inhibitors were selected as 1L in 64.1% of *BRAF* ^{V600}-Mut. Median follow up was 18.3 months (m) (95% CI 17.1-19.6). Median overall survival (OS) was (estimated) 28.1 m (95% CI 22.9-NA). With 1L CPi, 12 and 18-m OS was 79.4% and 70.5% respectively for *BRAF*-wt group and 90.2% and 82% for *BRAF* ^{V600}-Mut (median OS not reached in either group). In pts with *BRAF* ^{V600}-Mut and TT, 12 and 18m OS was 62.4% and 50.9% respectively and median OS 18.5m (95% CI 13.3-28.1). OS according to ECOG, LDH and M1 stage is in the table G3-4 AEs appeared in 7.9% of pts treated with TT and 9.2% with CPi.

Table: 1056P

	Factor		%	% 12 - 18 m OS *p (Cox/log-rank) <0.05
BRAF ^{V600} Mut TT	ECOG	0-1 vs >1	77/33	**67.5 - 56.4* vs** 44 - 35
	LDH	≤ULN vs >ULN	53/47	**78 — 63* vs** 46.7 - 39.8
	M1	a-b vs c-d	59/41	**75.6 — 71* vs** 53.1 - 37
BRAF ^{V600} Mut CPi	ECOG	0-1 vs >1	98/2	90.2 - 85.2 vs NA
	LDH	≤ULN vs >ULN	72/28	88.5 - 88.5 vs 90 - 80
	M1	a-b vs c-d	55/45	84.2 - 84.2 vs 91.3 - 82.6
BRAF wt CPi	ECOG	0-1 vs >1	89/11	**83.9 - 74.9* vs** 46.2 - 30.8
	LDH	≤ULN vs >ULN	66/34	**89 — 82* vs** 61.1 - 43.3
	M1	a-b vs c-d	56/44	**90.1 - 79.5* vs** 67.3 - 59

Conclusions: Survival of pts with advanced mel is similar to reported in clinical trials. 1L TT was chosen for 2/3 *BRAF* ^{V600}-Mut cases while 1/3 were treated with CPi. OS in pts treated with CPi seems superior to TT in *BRAF* ^{V600}-Mut group although potential bias must be considered since stage, LDH and ECOG impacted OS.

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1057P ROS1 mutation can serve- as a potential efficacious predictor of immunotherapy in melanoma patients

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Background: Melanoma is a serious skin cancer. Immune checkpoint inhibitors (ICIs) including atezolizumab, pembrolizumab, nivolumab, ipilimumab have shown durable responses and have been approved by FDA. However, ICIs demonstrate antitumor effects only in a fraction of patients, and research exploring the association between gene mutation and clinical benefit is limited. ROS1 mutation rate is high in melanoma. Studies have shown that ROS1 substitutions/indels correlated with higher TMB (Tumor Mutation Burden) and PD-L1+/TMB-H proportions than wild-type genotypes in NSCLC, which means that the mutation of ROS1 gene may be related to the efficacy of immunotherapy in patients with NSCLC, but the association between ROS1 mutation and TMB or survival in melanoma is unknown.

Methods: The association between ROS1 mutation with TMB and survival data was analyzed in melanoma patients from the public immunotherapy-treated cohort called Melanoma.Allen2015.WES.110, which worked as training cohort while the validation cohort1 was retrieved from Pancancer.Samstein2018.NGS.1661 and validation cohort2 was from Melanoma.Hugo2016.WES.38. Wilcoxon test was used for the comparison of TMB. Overall survival (OS) analyses were conducted in the public cohort using Kaplan-Meier curves and log-rank tests. Statistical significance was set at p=0.05.

Results: In the training cohort, 18.2% (20/110) melanoma patients harbored ROS1 mutation. ROS1 mutation is associated with higher TMB (p=0.00002). Survival analysis demonstrates that ROS1 mutation results in significantly longer OS (21.75 vs 7.65 months; HR, 0.55; p=0.046) in melanoma patients treated with ICIs. While the validation cohort1 shows that 20.1% (63/313) melanoma patients harbored ROS1 mutation,which results in an increasing trend on TMB with strongly significant difference (p=1.32*e-17)and significantly longer OS (19 vs 18 months; HR, 0.58; p=0.041). Besides, validation cohort2 also shows that ROS1 mutation results in an higher TMB with significant difference (p=0.017) and significantly longer OS (26.6 vs 14.4 months; HR, 0.25; p=0.045).

Conclusions: This study shows that ROS1 mutation is correlated with higher TMB in melanoma and serves as a predictive biomarker of ICI benefit in melanoma.

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1058P Treatment outcomes with unselected autologous tumor infiltrating lymphocytes (TILs) in patients (pts) with checkpoint inhibition–refractory advanced cutaneous melanoma

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Background: TIL products made from tumor digests showed a high overall response rate (ORR; 67%) and complete response (CR) rate (19%) and a safety profile consistent with lymphodepletion and high-dose interleukin (IL)-2 in a retrospective analysis of a single-center experience of TILs for compassionate use treatment of advanced cutaneous melanoma (n=21; Hawkins, et al. AACR 2021. ePoster LB150). This subanalysis assesses outcomes for pts who received TILs after prior checkpoint inhibition, a pt subset with limited treatment options.

Methods: Pts with metastatic cutaneous melanoma and no standard of care treatment options received lymphodepleting chemotherapy (cyclophosphamide ×2 d; fludarabine ×5 d) followed by TIL infusion and post-TIL high-dose IL-2. Safety was assessed by clinically significant adverse events (AEs). Efficacy assessments included ORR, CR rate, and overall survival (OS).

Results: Of 21 pts who underwent treatment between Oct 2011 and Aug 2019, 12 received prior PD-1 inhibitor (PD-1i) therapy and are reported herein. Median age was 55 y and 50% of pts were *BRAF*-mutated. Median no. of disease sites was 4, and 100% of pts had M1c or M1d disease (25% with M1d). All pts received prior CTLA-4i and all *BRAF*-mutated pts received prior BRAFi alone ± MEKi. The most commonly reported AEs post-TIL infusion were thrombocytopenia (75%), pyrexia (50%), and rigors (50%). No treatment-related deaths occurred. With a median follow-up of 45.5 mo, the ORR was 58% and the CR rate was 8%. At data cutoff, 2 pts (17%) had durable ongoing responses (>30 mo post-TIL infusion). Median OS in this subanalysis and in the overall population was 21.3 mo.

Conclusions: In this subanalysis of pts with relapsed advanced melanoma after both PD-1i and CTLA-4i, and for some, BRAFi, outcomes of unselected autologous TILs were similar to those observed in all treated pts, with high response rates and a safety profile consistent with that of TIL therapy. Unselected TILs may address the unmet medical need for the poor-risk subset of pts with advanced melanoma who experience disease progression following checkpoint inhibition and, if applicable, targeted therapy.

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1059P 18F-FDG-PET/CT response assessment in patients with advanced melanoma treated with combination of low-dose ipilimumab and anti-PD1: A real-world experience

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Background: Combination therapy with anti-PD1 and low-dose ipilimumab has shown reduced rate of immune-related adverse effects compared with standard dose used in the Checkmates studies 067 and 204. However, the discussion whether low-dose ipilimumab may hamper the response rate in advanced melanoma is still open.

Methods: We conducted a retrospective analysis of response evaluation based on 18F-FDG PET/CT for patients with advanced melanoma treated with combination of nivolumab 3mg/kg plus ipilimumab 1mg/kg for 4 cycles (N3+I1) followed by anti-PD1 maintenance therapy and compared the results to RECIST 1.1 response criteria in the same population.

Results: Between December 2017 and August 2020, 45 patients with advanced melanoma treated with N3+I1 in first-line setting were identified.
Unresectable stage III/stage IV were 2/43 patients, respectively. Among stage IV patients, 60.5% were M1c, 23.3% had elevated LDH and 28% had brain metastasis (3 or more brain lesions: 58%). At a median follow-up of 16.7 months, 11 patients (24.4%) had G3/G4 toxicity. During induction phase, three patients (6.6%) discontinued all drugs and 2 other patients (4.4%) interrupted only ipilimumab. Review of response evaluation by RECIST was possible in 36 patients and showed an objective response of 50%. Complete response (CR): 11% and partial response (PR): 39%. Eight percent presented progressive disease (PD). In 37 patients, review of response evaluation using 18F-FDG PET/CT was possible. Twenty-four patients (65%) achieved metabolic CR, 5 (13.5%) PD and 8 (21.5%) were classified as non-CR non-PD. Median progression-free survival (PFS) and overall survival (OS) were not reached. 12-month PFS and OS were: 72.5 and 89%, respectively. During the study follow-up, only 1 patient with metabolic complete response relapsed and 3 out of 8 with non-CR non-PD progressed.

Conclusions: Using low-dose ipilimumab combination does not hamper the response rates and, possibly due to fewer protocol interruptions, these patients may achieve more complete responses as showed by 18F-FDG PET/CT evaluation.

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1060P Serum metabolomic profiling reveals differences in polyamine and tryptophan metabolites in patients with cutaneous, mucosal and uveal melanoma

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Background: Patients (pts) with cutaneous melanoma (CM) have higher rates of response to immune checkpoint inhibitors (ICI) than pts with mucosal and uveal melanoma (MM/UM). Response to ICI is influenced by multiple factors, including the circulating levels of immunomodulatory metabolites. Accordingly, we sought to interrogate the serum metabolome of pts with CM, MM and UM to identify differences that could potentially influence this differential response to ICI.

Methods: This is an exploratory, retrospective observational study of pts with advanced melanoma treated with ICI. Metabolites were analyzed in serum samples collected before ICI therapy, and using a liquid chromatography mass spectrometry platform. Differences in metabolomics profiles were compared using Random Forest (RF), Multidimensional scaling (MDS), and Kruskal-Wallis test. Overall survival (OS) was assessed using Kaplan-Meier, Log-Rank, and Cox regression models. Statistical significance was set to 0.05.

Results: Serum levels of 115 metabolites in 13 CM, 12 MM and 11 UM pts were analyzed. MDS analysis indicated distinct metabolomic profiles amongst the three melanoma subtypes. Using RF analysis, high levels of Hydroxykynurenine (HKyn) distinguished MM and UM from CM. Further interrogation revealed CM had lower HKyn ($p<0.001$) and higher Kynurenic Acid ($p<0.028$) compared to MM and UM. UM, the most ICI-resistant melanoma subtype, was associated with higher levels of the polyamine spermine (SPM) compared to CM and MM ($p=0.029$). This finding suggests that high SPM may correlate with resistance to ICI, potentially across melanoma subtypes. Indeed, in our CM cohort of patients, lower SPM had a trend toward longer median OS (12.8 vs 6.1 months, $p=0.258$) on treatment with ICI. This was validated in external published cohort, including 78 patients with advanced CM melanoma treated with ICI, as lower plasma SPM was associated with increased mOS, 24.9 vs 11.1 months ($p=0.020$).

Conclusions: These data indicate altered polyamine metabolism and high circulating levels of SPM identified as a feature of the UM, and distinct kynurenine metabolism in all three melanoma subtypes which may influence their response to ICI. Validation of these data in larger cohorts is still required.

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1061P Safety of cemiplimab for advanced cutaneous squamous cell carcinoma: The Spanish named patient programme

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Background: Cemiplimab is a programmed cell death receptor-1 inhibitor with anti-tumour activity for cutaneous squamous cell carcinoma (CSCC) and acceptable safety proved in its pivotal trial. We provide the first data on cemiplimab safety in daily practice from the named patient programme (NPP) for advanced CSCC in Spain.

Methods: This cemiplimab NPP was performed from March 2019 to March 2020. It included patients aged ≥18 years with advanced CSCC and ineligible for surgery, radiation therapy or clinical trials. The cemiplimab safety was assessed according to treatment-emergent adverse events (TEAEs) reported until March 2021.

Results: 140 patients were included (median age [interquartile range, IQR] 77.0 [65.0-84.0] years; age ≥80 38%; men 71.7%; ≥1 comorbidity 83%; ECOG 0-1 86.3%; locally advanced CSCC 60.7%; cemiplimab as first-line therapy 67.7%). Cemiplimab was received for a median (IQR) of 8.0 (3.0-14.0) cycles. Fifty-eight (41.4%) patients showed ≥1 of the 163 TEAEs reported, which most frequently included diarrhoea n=7, asthenia n=6, constipation n=4 and abdominal pain n=4. Fourteen (8.6%) were immune-mediated, mainly bronchitis n=2, pneumonitis n=2 and hepatitis n=2. Seventy-eight (47.9%) TEAEs were grade ≥3, most frequently pneumonia n=3, COVID-19 n=3, general physical health deterioration n=2, pyrexia n=2, renal transplant failure n=2, sepsis n=2, acute kidney injury n=2 and respiratory failure n=2. Twenty-one (12.9%) were treatment-related (TREAEs): 11 (6.7%) were grade 1-2 (diarrhoea n=3 and asthenia, hepatotoxicity, malnutrition, odynophagia, polymyalgia rheumatica, pneumonitis, pruritus, and skin toxicity), 9 (5.5%) grade 3 (acute kidney injury, adrenal insufficiency, abdominal pain, blood creatinine increased, dysphagia, haematuria, immune-mediated enterocolitis, panniculitis, surgical wound infection) and 1 (0.6%) unknown grade. Cemiplimab was withdrawn due to TREAEs in only 5 (3.6%) patients. The TEAE outcome was fatal in 29 (17.8%); none related to cemiplimab.

Conclusions: This NPP supports the real-life safety of cemiplimab for CSCC, showing an acceptable safety profile consistent with previous reports.

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1062P Real-world data on clinical outcome and tolerability in patients with advanced cutaneous squamous cell carcinoma treated with cemiplimab in the Netherlands

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Background: Cutaneous squamous cell carcinoma (CSCC) is the second most common cutaneous malignancy and patients with locally advanced or metastatic disease have a poor prognosis. Cemiplimab, a monoclonal anti-PD-1 antibody, has recently been approved by the FDA and EMA for this patient cohort based on single-arm phase II studies. Real-world data on clinical outcome and tolerability is still scarce.

Methods: In this retrospective cohort analysis, patients treated with cemiplimab for advanced CSCC from 3 sites in the Netherlands from November 2018 until August 2020 were evaluated for response and toxicity. Collected data comprised patient's demographics, tumor characteristics and treatment course. Clinical response, adverse events (AE), progression-free survival (PFS) and overall survival (OS) were assessed.

Results: In total, 66 patients (50 male, 16 female, median age 75; range 30-93 years) with unresectable locoregional (41 (62%) patients) or metastatic (25 (38%) patients) CSCC treated with flatdose cemiplimab 350mg Q3W were included. All but 8 patients (88%) had severe comorbidities, the most common site of the primary tumor was the head or neck (79%) and 7 (11%) patients were pretreated with systemic therapy. A median of 6.5 doses of cemiplimab (range 1-31 doses) were administered and treatment was well-tolerated, with grade 1-2 AEs in 70% and grade 3-4 AEs in 17% of patients. An objective clinical response was seen in 33 (50%) patients, of whom 9 (14%) reached CR and 24 (36%) PR. With a median follow-up of 11.7 months (95% CI 8.4-15.0 months), median PFS was 17.3 months and median OS was not reached. In 39 (59%) patients treatment was discontinued, mostly due to disease progression (49%). In 8 (21%) patients with ongoing response treatment was stopped after a median of 11.5 months (range 2.9-15.2 months).

Conclusions: In this real-world cohort of advanced CSCC patients, cemiplimab demonstrated to be well-tolerated, achieving an objective clinical response in 50% of patients, even in elderly patients with severe comorbidities. Their outcome was comparable to the results of prospective clinical trials.

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1063P Real-world treatment patterns and outcomes of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) in the US

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Background: There are limited published real-world data on the treatment patterns and outcomes of patients with mCSCC.

Methods: This retrospective study was conducted using IBM MarketScan® Commercial and Medicare databases (1 Jan 2013–31 Jul 2019). We identified patients ≥18 years of age with a CSCC diagnosis initiating systemic treatment at index date between 1 Jan 2014 and 31 Dec 2018, and who were continuously enrolled for ≥12 months prior to the index date. Eligible patients had evidence of mCSCC during the baseline period; no surgery or radiotherapy (RT) on or 90 days after index date; <3 claims diagnostic codes of lung, head and neck or anogenital squamous cell carcinomas 180 days prior to the index date; and no immunotherapy during follow-up (FU). FU was from the index date to disenrollment, death or end of study.

Results: A total of 207 patients met the inclusion criteria. Mean (standard deviation [SD]) age was 64.8 (13.4) years; 76.3% were male; 59.4% had prior radiotherapy; and 58.9% had prior CSCC related surgery. Mean (SD) FU time was 16.3 (14.3) months. During FU, 75.4%, 51.7% and 36.2% of patients received chemotherapy, RT, or targeted therapy as first-line (1L) treatment. Mean (SD) of duration of 1L therapy was 61.6 (66.5) days. Cisplatin (32.9%) and carboplatin (22.7%) were the most common chemotherapy agents and cetuximab (32.4%) the most common targeted therapy. Median (95% confidence interval) overall survival (OS) as observed during the FU period was 12.1 months (10.4—16.8). OS at 6 and 12 months were 76% and 50%, respectively. In the FU period, 98.6% patients had a CSCC-related outpatient (OP) visit. Mean (SD) CSCC-related healthcare costs in the FU period were $5,354 ($8,945) per person per month (PPPM), with 96.4% attributable to OP costs. Mean (SD) OP costs for RT were $1,589 ($3,374) PPPM. Mean (SD) OP ($31 [$109] PPPM) and inpatient ($23 [$243] PPPM) surgical procedure costs were low.

Conclusions: During the period of this analysis, cisplatin and cetuximab were the most common systemic therapies used in the 1L setting. The prognosis of patients with mCSCC was generally poor. Most CSCC related healthcare costs were due to OP costs.

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1064P Final results of CA209-9JC: A phase II study of first-line nivolumab in patients with advanced cutaneous squamous cell carcinoma

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Background: Immune checkpoint blockade has emerged as a novel treatment option for patients (pts) with advanced cutaneous squamous cell carcinoma (AcSCC). Here, we present the final results of a single-arm, phase II study of the anti-PD-1 agent nivolumab (NIVO) in pts with advanced AcSCC.

Methods: Systemic therapy-naïve pts with AcSCC not amenable to complete resection or radiation were treated with NIVO 3mg/kg every 2 weeks until disease progression, unacceptable toxicity or 12 months (mo) of treatment. The primary endpoint was the best objective response rate (bORR) as per RECIST 1.1 criteria. Secondary endpoints included safety, progression-free survival (PFS) and overall survival (OS).

Results: Between October/2018 and October/2019, 24 pts with AcSCC were included, with a median age of 74 years (range 48-93). Most frequent primary sites were head/neck (41.7%) and trunk (29.2%), and 41.7% of the pts had received prior radiation-therapy. Locoregional disease (n=16; 66.6%) was the most common presentation, followed by locally advanced and metastatic disease (n=4; 16.6% each). The majority of pts (54.2%) completed 12 months of treatment with NIVO and entered active surveillance, and 37.4% developed disease progression while on treatment. All 24 pts were evaluable for response at this final analysis, and the bORR was 58.3% (14/24); 20.8% of the pts had progressive disease as the best response. Median duration of response has not been reached; median PFS was 12.7mo and estimated median OS was 20.7 mo. In univariate analyses, prior exposure to radiation therapy was associated with worse outcomes (p=0.035). Treatment-related AEs of any grade occurred in 21 pts (87.5%), and the most frequent were hypothyroidism, pruritus, lymphopenia, fatigue and arthralgias. Grade ≥3 treatment-related adverse events occurred in 6 pts (25%), and 1 patient discontinued NIVO due to toxicities.

Conclusions: NIVO demonstrated pronounced antitumor activity and durable responses in systemic-treatment-naïve pts with AcSCC, with a favorable tolerability even in pts at advanced ages. These results reinforce the role of anti-PD-1 agents as standard treatment options for this disease.

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1065P A retrospective multicenter Italian analysis of the effect of longer vismodegib intake in 68 basal cell carcinoma patients who achieved clinical complete remission

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Background: The management of Basal Cell Carcinoma (BCC) patients (pts) experiencing clinical complete remission (cCR) upon HedgeHog Inhibitors (HHIs) has not been defined yet. We evaluated whether time to HHI stop after cCR is associated to better recurrence-related outcomes.

Methods: A retrospective, observational, Italian analysis was conducted in 7 onco-dermatology centers. BCC pts treated with HHI (vismodegib) from 2012 to 2019, who had achieved cCR, were considered. We analyzed the n. of Days of Treatment needed to achieve cCR (DTCR), To vismodegib Stop after cCR (DTS), the Total Treatment Days (TTD = DTCR+DTS), and the Disease-Free Survival (DFS) as the n. of days from cCR to recurrence (or to last follow-up in not recurrent patients). Reasons to stop vismodegib were classified as R1) Toxicity; R2) disease recurrence. The relationship between DTCR, DTS, and DFS in the whole population and in the R1 subgroup was assessed by Pearson's correlation coefficient ($p<0.05$).

Results: Pts' characteristics and main results are reported in the table. Among 68 BCC pts experiencing cCR, 21% (n=14) stopped early vismodegib (≤2 months, mo) while 79% (n=54) were on HHI longer (>2 mo). Thirty-eight (56%) pts recurred with a median (m) DFS of 357 (60-1792) days (d). In the R1 subgroup, 26 (52%) pts recurred. While the DTCR was not correlated to DFS, DTS and TTD significantly correlated to DFS, both in the whole population ($p<0.0001$ and $p<0.0001$, respectively), and only in the R1 subgroup (n=50, p=0.0002 and p=0.0009, respectively). In recurrent pts (n=38), DTS correlated to DFS (p=0.0056), also when considering only the R1 cohort (n=28, p=0.0002). Pts who prolonged vismodegib >2 mo after cCR had higher DFS compared to those ≤2 mo (mDFS 470 vs 174d, p=0.008).

Table: 1065P

Pts characteristics and main results		N (range or %)
Median age		75.5 (39-100)
Sex	Male	43 (63)
	Female	25 (37)
Disease subsite	Head/neck	51 (75)
	Other	17 (25)
Disease stage	Locally advanced	65 (96)
	Metastatic	3 (4)
Gorlin syndrome	yes	12 (18)
	no	56 (82)
Stop Vismodegib	yes	61 (89)
	no	7 (11)
Stop Vismodegib reason	R1	50 (82)
	R2	11 (18)
Median DTCR		180 d (56-595)
Median DTS		125 d (0-1018)
Median TTD		403.5 d (95-2112)
Median follow-up		414.5 d (0-2600)

d= days

Conclusions: A prolonged intake of vismodegib after cCR achievement might improve the recurrence-related outcomes in BCC pts.

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1066P Extended-dose cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC): Primary analysis of phase II results

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Background: Cemiplimab 350 mg every 3 weeks (Q3W) intravenously (IV) is a standard of care for advanced CSCC. For some patients and physicians, extended dosing may allow flexibility in treatment management. Here, we present the primary analysis of data from cemiplimab 600 mg every 4 weeks (Q4W) IV in advanced CSCC. Pharmacokinetics (PK) modelling indicated that this dosing regimen would maintain cemiplimab C_{trough} at the level of the approved Q3W regimen.

Methods: Patients received cemiplimab 600 mg Q4W IV for up to 48 weeks and tumour assessments every 8 weeks. The primary endpoint was ORR by independent central review (ICR) per RECIST 1.1 and/or modified WHO criteria. Key secondary endpoints included duration of response (DOR), complete response (CR) rate and the PK and safety profiles of cemiplimab. Data cut-off was 18 April 2020.

Results: Sixty-three patients were enrolled (mCSCC, n=39; laCSCC, n=24; median age, 74 years; male, 84%; 14% had received prior systemic therapy). With median follow-up of 9.2 months (range: 1.0—16.5), ORR by ICR was 58.7% (95% CI: 45.6—71.0) with a CR rate of 17.5%. Median DOR had not been reached; Kaplan—Meier estimation of ongoing response at 12 months was 89.4% (95% CI: 70.0—96.6). Durable disease control rate was 76.2% (95% CI: 63.8—86.0). Median progression-free survival per ICR and overall survival had not been reached. Extended-dose cemiplimab resulted in observed mean (SD) C_{max} of 281 (235) mg/L and C_{trough} of 62.5 (24.1) mg/L. The most common treatment-emergent adverse events (AEs) were diarrhoea, pruritis (each n=15; 23.8%) and fatigue (n=14; 22.2%). Investigator-assessed Grade ≥3 immune-mediated AEs occurred in eight (12.7%) patients.

Conclusions: Significant efficacy of cemiplimab 600 mg Q4W IV (ORR 58.7%, CR 17.5% per ICR) was demonstrated, in line with that of the approved Q3W regimen. No new safety signals are observed, and the PK data confirm maintenance of C_{trough} levels seen with the 350mg Q3W IV regimen.

Clinical trial identification: NCT02760498.

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1067P Correlation between the number of risk factors and relapse in patients with cutaneous squamous cell carcinoma: A predictive factor for accurate adjuvant radiotherapy?

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Background: Despite clinical and histopathological factors are associated with high-risk cutaneous-squamous cell carcinoma (cSCC), equivocal definition for high-risk cSCC patients is lacking and their management remains challenging. We aim to identify factors predicting relapse in cSCC patients treated with surgery, combined or not with radiotherapy (RT) and to assess if adjuvant RT was associated with benefits in PFS.

Methods: This retrospective analysis included patients with resectable cSCC treated with surgery and/or RT in curative intent, at Centre Léon Bérard (Lyon, France) from April 2010 to September 2020. Independent predictive factors for relapse were searched using Cox regression analyses. The benefit of adjuvant RT was assessed according to the number of risk factors. PFS was estimated using the Kaplan-Meier method. Lesions were used as statistical units.

Results: A total of 303 patients with 529 cSCC were included. The median number of lesions per patient was 3 (1-25). With a median follow-up of 54 (0.2-126) months, 103 cSCC relapsed. The multivariate analysis identified as predictive factor for relapse in cSCC treated with exclusive surgery, the number of risk factors (HR 15.110 [3.91-58.40] for $\geq$3 risk factors, HR 4.497 [1.47-13.76] for 1 risk factor, p$<$0.001), low differentiation (HR 4.930 [2.47-9.86], p$<$0.001) and perineural involvement (HR 2.442 [1.11-5.38], p=0.027). Deep invasion, location, and tumour size were not significantly associated with higher risk of relapse. 31 cSCC were treated with surgery and adjuvant RT. Considering cSCC with equal number of risk factors, cSCC treated with surgery and adjuvant RT tended to associate with better PFS than cSCC treated with surgery alone (HR 0.47 [0.20-1.14], p=0.087). In the subgroup of cSCC with $\geq$3 risk factors, a significantly better PFS is observed in cSCC treated with surgery and adjuvant RT compared with those treated with exclusive treatment (p=0.0283).

Conclusions: Increased number of risk factors identified as a predictive factor of relapse in cSCC. Adjuvant RT improved PFS in cSCC with $\geq$3 risk factors.

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1068P Efficacy of combined hypo-fractionated radiotherapy (RT) in anti-PD-1 monotherapy-treated melanoma pts

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Background: Information on RT in anti-PD-1-treated melanoma pts is limited.

Methods: Search for all pts with unresectable AJCC stages III-IV melanoma initiating anti-PD-1 without ipilimumab between 1/1/15-30/8/19 in a prospective database of a referral center. Radiologists evaluated radiated and non-radiated lesions (RECIST 1.1) every 3 m. Main criteria were the complete response (CR) rate. Overall (OS) and progression-free (PFS) survivals were calculated using Kaplan-Meier. Multivariate analysis studied factors associated with CR or partial response (PR). Database lock: 30/11/20.

Results: 206 pts (59% M1c/d, 50% $\geq$3 metastasis sites, 33% ECOG PS$\geq$1, 33% $>$1 line, 32% LDH$>$ULN) received nivolumab (83%) or pembrolizumab (17%). Median follow-up was 19.5 m. A total of 100 pts (49%) received first RT early ($<$3 m of PD-1 blockade, in 39 pts with rapidly progressing lesions) or late ($>$3 m, in 61 pts with confirmed non-response to anti-PD-1 therapy). First RT was hypo-fractionated RT to 1-2 targets (26 Gy in 4 weekly radiations (68 pts), radiosurgery (SRS) for brain mets (25 pts), or standard RT. 39 pts received a second RT. Globally, 66 (32% [95%CI:25.7-38.4]) pts achieved CR (with anti-PD-1 discontinuation in 64 pts, with 9 pts (14%) relapsing to date). RT added 24 CR to the 42 CR observed without. Median PFS and OS were 15.6 [95%CI: 10.7-22.8] and 24.6 [16.9-41.8] m, respectively. In pts with P, PFS and OS were 16.6 [13.2-25.0] and 36.4 m[24.2-NA], respectively, in radiated pts and 2.4[2.2-3.5] and 4.9 m[2.6-7.7], respectively, in non-radiated pts (P$<$0.001). In radiated pts, rates for radiated lesions of CR, PR, stable (SD), progressive (PD) disease were 26%, 26%, 8%, and 37% (non-evaluable:3%), respectively, and 24%, 14%, 1%, and 61%, respectively, for non-radiated lesions. Abscopal response was observed in non-radiated lesions in 30% of pts radiated late for non-response to anti-PD-1. AJCC staging, naïve vs non-naïve, ECOG PS, LDH serum level, $<$3 sites with metastasis vs $\geq$3, oligo vs multimetastatic disease, hypo-fractionated RT vs SRS, early vs late RT were not associated with CR+PR in radiated patients. No unusual adverse event was seen.

Conclusions: High-fraction doses RT may enhance anti-PD-1 efficacy and CR rate above the 15-21% seen in registration studies.

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1069P Granulomatous and sarcoid-like immune adverse events following CTLA4 and PD1 blockade adjuvant therapy of high-risk melanoma: A combined analysis of ECOG-ACRIN E1609 and SWOG S1404 phase III trials

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Background: Treatment with immune checkpoint inhibitors (ICIs) has been linked to granulomatous and sarcoid-like lesions (GSL) affecting the skin, lungs, thoracic lymph nodes, eyes and other organs. Accurate diagnosis and reporting of such rare events are essential to clinical practice and patient care.

Methods: We recently reported an estimated incidence of GSL among a subset of patients treated with adjuvant ipilimumab. In this analysis, we expanded our cohorts to include patients enrolled in the phase III adjuvant trials E1609 (N=1670) that

tested ipilimumab 3 mg/kg (ipi3) and 10 mg/kg (ipi10) versus high-dose IFN-α (HDI) and S1404 (N=1207) that tested pembrolizumab versus patient/physician choice of ipi10 or HDI. We sought to estimate the incidence of GSL as reported by trial investigators in the combined datasets utilizing descriptive statistics as summarized in the table, along with the corresponding CTCAE grades.

Results: Among 2878 patients treated with ICIs or with HDI in E1609 and S1404, 523 were treated with ipi3, 932 with ipi10, 640 with pembrolizumab and 783 with HDI. A total of 11 GSL cases were reported. Cases were reported with ipi10, followed by pembrolizumab, ipi3 and HDI, respectively. Organs involved included skin and subcutaneous tissue (granuloma annulare, granulomatous dermatitis), eye (ocular sarcoidosis), lymph nodes (noncaseating granulomatous lymphadenitis), lung and mediastinal lymph nodes (sarcoidosis, granulomatous inflammation).

Table: 1069P

	Organ(s) involved	Ipi3 (N=523)	Ipi10 (N=932)	Total Ipi (N=1455)	HDI (N=783)	Pembrolizumab (N=640)
E1609	Ocular	-	1 (Gr 2)	1	-	NA
	Skin	-	1 (Gr 1)	1	-	NA
	Lung and lymphatic	1 (Gr 3)	2 (Gr 3 x2)	3	1 (Gr 3)	NA
S1404	Skin	NA	1 (Gr 1)	1	-	-
	Lymphatic	NA	-	-	-	1 (Gr 1)
	Lung and lymphatic	NA	1 (Gr 2)	1	-	2 (Gr 1, Gr 3)
	Total (%)	1 (0.19%)	6 (0.64%)	7 (0.48%)	1 (0.13%)	3 (0.47%)

Conclusions: Granulomatous and sarcoid-like lesions (GSL) following adjuvant anti-CTLA4 and anti-PD1 antibody therapy in high-risk melanoma were reported rarely. Reported cases ranged in grade from 1-3 and appeared manageable. Careful attention to these events and their reporting would be essential to better guide practice and management guidelines.

Clinical trial identification: E1609 trial was coordinated by the ECOG-ACRIN Cancer Research Group and supported by the United States National Cancer Institute (NCI) of the National Institutes of Health (NIH). S1404 trial was coordinated by the SWOG Cancer Research Group and supported by the Unites States National Cancer Institute (NCI) of the National Institutes of Health (NIH).

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1070P Adjuvant treatment for melanoma in clinical practice: Trial versus reality

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Background: Little is known about outcomes of adjuvant-treated melanoma patients beyond the clinical trial setting. Since 2019, adjuvant-treated melanoma patients have been registered in the DMTR, a population-based registry to monitor the quality and safety of melanoma care in the Netherlands. This study aims to describe treatment patterns, relapse, and toxicity rates of adjuvant-treated melanoma patients beyond the clinical trial setting.

Methods: Analyses were performed on adjuvant-treated melanoma patients included in the DMTR. Descriptive statistics were used to analyze patient-, and treatment characteristics. A baseline registration completeness analysis was performed, and an analysis on trial eligibility in clinical practice patients. Recurrence-free survival (RFS) at 12-months was estimated with the Kaplan-Meier method.

Results: A total of 683 patients treated were treated with adjuvant systemic therapy. The majority (93.9%) of these patients were treated with anti-PD-1. RFS at 12-months was 69.7% (95% CI, 65.8-73.9) with a median follow-up of 12.2 months. Factors associated with RFS were stage of disease and Breslow thickness. Eighteen percent of the anti-PD-1-treated patients developed grade ≥3 toxicity. Sixty-one percent of patients prematurely discontinued anti-PD-1 therapy.

Conclusions: Adjuvant anti-PD-1 treatment of resected stage III/IV melanoma in daily practice showed higher toxicity rates and more frequent premature discontinuation but similar RFS rates compared to trials.

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1071P A nationwide, real-life study of outcome and quality of life after the introduction of adjuvant immunotherapy for Danish melanoma patients

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Background: Clinical trials have shown promising results for adjuvant immunotherapy in resected stage III-IV melanoma patients, but real-life data are scarce. Data on efficacy and quality of life (QoL) during anti-PD-1 adjuvant therapy from a complete national cohort of melanoma patients may support treatment choices and help patient guidance.

Methods: Patients with stage III-IV resected melanoma have been registered in The Danish Metastatic Melanoma Database (DAMMED) since the introduction of adjuvant immunotherapies in Denmark in Nov 2018. Patient characteristics, treatment, outcome data, and pathology results were included. EORTC QLQ-C30 was submitted to all patients who had not relapsed at the cutoff date 31 Dec 2020, and patients were divided into cohorts based on time elapsed from treatment initiation.

Results: Between Nov 2018 and Jan 2021, 546 patients were treated with adjuvant nivolumab. At baseline, 91.6% of patients had cutaneous melanoma, 86.8% had an ECOG performance score of 0, 82.4% had normal LDH level, 85.0% had stage III resected melanoma, and median age was 62 years (range 16-86). With a median follow-up of 14.2 months (95% CI 12.9-15.3), 25.5% of patients had relapsed and 5.3% had died. 1-year recurrence-free survival (RFS) and overall survival (OS) were 75.5% (71.1-79.3) and 95.1% (92.5-96.9), respectively, and 2-year RFS and OS were 56.0% (47.7-63.1) and 91.4% (87.6-94.1). For 292 patients with a follow-up >12 months, the median number of cycles of nivolumab administered was 11 (range 1-13). A total of 135 patients finalized planned therapy (46%), 80 patients discontinued due to toxicity (27%), 67 patients due to relapse (23%), and 10 patients due to other reasons (4%). 263/405 (64.9%) patients completed the EORTC QLQ-C30 questionnaire. A drop in median global health score was observed in responding patients between 3-6 months after treatment initiation (n=45), compared to patients at 0-3 months (n=26) or >15 months (n=103).

Conclusions: Half of all real-world melanoma patients from an entire national cohort undergoing adjuvant therapy with nivolumab stopped the planned 1-year treatment prematurely due to either toxicity or relapse. A questionnaire revealed a temporary drop in QoL.

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1072P Primary ipilimumab/nivolumab immunotherapy 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. We investigate the efficacy of Ipilimumab/Nivolumab combination as primary treatment of locally advanced or oligometastatic melanoma patients (pts), within an open label, single arm study.

Methods: Treatment 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, degree of immune activation; evaluation of microbioma.

Results: 35 pts were treated within the trial: 3 pts are still in neoadjuvant therapy, 3 pts were discontinued before surgery (due to toxicity, progression and consent withdrawal) and 29 pts concluded neoadjuvant therapy after 4 (26 pts), 3 (2 pts) and 2 (1 patient) cycles and underwent surgery. pCR was reached in 16 (55%), near pCR in 2 (7%), pathological partial remission in 4 (14%) and pathological no response (pNR) in 4 (14%) pts. 21 pts concluded the adjuvant therapy. With a median follow-up of 12 months, 34 pts are alive. Relapses occurred in 1 patient after the 4 courses of neoadjuvant and in 4 pts (1 pCR and 3 pNR at surgery) during/after adjuvant therapy. 6 pts (17%) developed related G3-4 adverse events (AE): 3 transaminitis, 1 pneumonitis, 1 myocarditis and 1 CPK increase; all of them but one underwent to surgery after toxicity resolution. One patient died 5 months after the end of therapy due to ischemic stroke.

Conclusions: Neoadjuvant Ipilimumab/Nivolumab followed by adjuvant nivolumab is safe and able to achieve a pCR/near pCR rate of 62%. Toxicity was lower than that

already observed with this schedule. Translational data on potential genomic biomarkers of response, gut microbiome and systemic inflammatory landscape evaluated longitudinally on each patient will be presented at ESMO.

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1073P Quality of life (QOL) endpoints from the phase III intergroup S1404 adjuvant melanoma trial

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Background: A key issue for adjuvant melanoma patients is how they weigh the potential benefits of treatment and QOL. We assessed QOL in S1404, a trial of adjuvant pembrolizumab versus either high-dose interferon-alfa 2b (HDI) or ipilimumab.

Methods: QOL was required for patients able to complete questionnaires in English, Spanish, or French and was obtained on treatment at cycles 1, 3, 5, 7, 9 (corresponding to weeks 4, 13, 25, 37, 49) using the Functional Assessment of Cancer Therapy (FACT) Biological Response Modifiers (FACT-BRM), FACT-General (FACT-G), Functional Assessment of Chronic Illness Therapy-Diarrhea (FACIT-D), and the EuroQol EQ-5D-3L scales. The primary endpoint was the cycle 3 FACT-BRM trial outcome index (TOI). Linear regression was used to compare FACT-BRM TOI scores by arm. Linear mixed models were used to evaluate QOL scores over time, with pattern mixture models performed to account for missing data. Regression analyses included adjustments for the baseline score, disease stage and PD-L1 status. Based on the literature, a clinically meaningful difference of 5 points was targeted.

Results: Among 1303 eligible patients, 1188 (91.1%) had baseline FACT-BRM TOI scores. Patients were predominantly $<$65 years (74.2%) and male (59.5%); 82.4% had positive PD-L1 status. For the primary endpoint, 842 patients were evaluable (ipilimumab/HDI, 267; pembrolizumab, 565). Estimates of FACT-BRM TOI cycle 3 compliance did not differ by arm (ipilimumab/HDI, 96.0% vs. pembrolizumab, 98.3%, $p=0.25$). The adjusted cycle 3 FACT-BRM TOI score was 9.6 points (95% CI, 7.9 to 11.3; $P<0.001$) higher (better quality of life) for patients on the pembrolizumab arm compared to the ipilimumab/HDI arm, exceeding the pre-specified clinically meaningful difference. In longitudinal analyses, differences by arm exceeded 5 points in favor of pembrolizumab for each cycle except cycle 9. Results were consistent in pattern mixture models. In post-hoc analyses, FACT-BRM TOI scores favored the pembrolizumab arm compared to patients receiving either adjuvant HDI (17 points, 95% CI, 14.6-19.4, $p<0.001$) or ipilimumab (6 points, 95% CI, 4.1-7.8, $p<0.001$).

Conclusions: Adjuvant pembrolizumab results in an improved QOL over adjuvant HDI or ipilimumab.

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J.M. Kirkwood: Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Advisory Board: Bristol Myers Squibb; Financial Interests, Personal, Advisory Board: CheckMate; Financial Interests, Personal, Advisory Board: Harbour BioMed; Financial Interests, Personal, Advisory Board: Iovance; Financial Interests, Personal, Advisory Board: Istari; Financial Interests, Personal, Advisory Board: OncoSec; Financial Interests, Personal, Advisory Board: Novartis; Financial Interests, Personal, Advisory Board: Pfizer; Financial Interests, Personal, Advisory Board: Elsevier; Financial Interests, Personal, Advisory Board: OncoCyte; Financial Interests, Personal, Advisory Board: Takeda; Financial Interests, Personal, Advisory Board: Immunocore; Financial Interests, Personal, Advisory Board: Natera; Financial Interests, Personal, Proprietary Information, Data Safety Monitoring Board: Cytel. V. 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1074P Italian nivolumab Expanded Access Program (EAP) in melanoma adjuvant setting: Patients outcomes and safety profile

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Background: At a minimum of 4 years' follow-up, nivolumab demonstrated sustained recurrence-free survival (RFS) benefit versus ipilimumab in resected stage IIIB–C or IV melanoma remaining an efficacious adjuvant treatment with a tolerable safety profile (Ascierto et al. ESMO 2020). The purpose of this analysis is to evaluate if nivolumab use in real world setting confirms the clinical trial data.

Methods: From November 2018 to June 2019 we enrolled 612 patients (pts) with stage III and IV resected melanoma to receive nivolumab as part of an Italian BMS EAP. Patients received intravenous nivolumab 3 mg/kg or 240 mg Q2 weeks or 480 mg Q4 weeks to a maximum of 12 months (62% male and 38% female, median age 60 years (16-86), 420 BRAF WT, 156 BRAF mutated, 36 unknown). Among 612 pts, 77%

were stage III (IIIA: 122, IIIB: 132, IIIC: 213, IIID: 4) and 23% were stage IV NED (CM238: IV NED 18%). Most pts had a cutaneous melanoma (89%), 3 uveal and 16 mucosal melanoma. 47 melanomas were of unknown origin. Tumor ulceration was present in 27% of pts.

Results: At the data cut-off of March 2021, 63% of the pts completed 1-year treatment. With a median follow-up of 18 months (IQR 14-21) and a median number of doses of 22 (1-28), the results are the following:

Table: 1074P

	RFS 12mos - 18mos (%)		DMFS 12mos - 18mos (%)	
	EAP	CM238	EAP	CM238
ITT	77 - 67	70 - 66	84 - 76	-
BRAF WT	75 - 65	72 - 66	83 - 73	-
BRAF MUT	83 - 74	68 - 65	87 - 81	-
ST. III	81 - 70	72 - 67	84 - 76	80 - 75
ST. IIIA	87 - 80	-	92 - 87	-
ST. IIIB	86 - 72	-	89 - 76	-
ST. IIIC	71 - 60	-	80 - 71	-
ST. IV	71 - 63	63 - 61	79 - 73	-

Among 612 pts, 10% discontinued treatment due to toxicity. Treatment-related grade 3 or 4 adverse events were reported in 11% of pts and 3 (0.5%) treatment-related deaths (rhabdomyolysis, diabetic coma and intestinal hemorrhage) were observed.

Conclusions: The results of this large clinical experience are in line with what reported in the pivotal clinical trial, despite the presence of some more unfavorable prognostic features. Although BRAF mutational status was not available for 36 pts, RFS in BRAF mutated pts was higher than that of CM238. According to these data, nivolumab confirms to be an effective/safe adjuvant treatment for resected stage III-IV melanoma pts, supporting its use in clinical practice.

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1075P Regression tree analysis to identify factors associated with relapse-free survival (RFS) in patients with resected stage III BRAF V600E/K–mutant melanoma

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Background: The 5-y analysis of the Phase III COMBI-AD trial (NCT01682083) showed long-term RFS benefit with 12 months of adjuvant dabrafenib (dab) plus trametinib (tram) vs placebo (pbo) in patients with resected stage III *BRAF* V600E/K–mutant melanoma (5-y RFS rate, 52% vs 36%; hazard ratio, 0.51 [95% CI, 0.42-0.61]). A prior regression tree analysis (median follow-up in the dab + tram arm, 44 mo) evaluated 13 patient and clinical characteristics to identify treatment type (dab + tram vs pbo), disease stage, and age as predictive of long-term benefit. We present an updated model that is based on the 5-y RFS data and incorporates additional variables.

Methods: This updated regression tree analysis (median follow-up, 60 mo) is evaluating baseline demographics, clinical characteristics, and biomarker parameters as candidate predictors for classification of patients enrolled in COMBI-AD (N = 870) into subgroups based on similar RFS. Patient and clinical characteristics included are age, sex, geographical region, *BRAF* V600 mutation type, body mass index, histological subgroup, T stage, N stage, number of positive lymph nodes, ulceration status, lactate dehydrogenase level, Eastern Cooperative Oncology Group performance status, time to treatment initiation, and treatment type. Biomarkers will include tumour mutational burden/landscape and gene expression signatures in baseline tissue samples generated by sequencing 570 genes and gene expression profiling with a NanoString® panel, respectively.

Results: A preliminary tree incorporating patient and clinical characteristics identified treatment type (dab + tram vs pbo), N stage, and T stage as important variables defining 5-y RFS subgroups. Evaluation of biomarkers for inclusion in the model is ongoing. Further refinements, including stability and goodness-of-fit analyses, are also in progress; the final tree will be presented.

Conclusions: These findings confirm and extend previous results using regression tree analysis to identify subgroups that may particularly benefit from adjuvant therapy. Such analyses may inform treatment decisions.

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1076P Real-world efficacy and safety data of immune checkpoint inhibitors in Turkish patients with metastatic melanoma: A Turkish oncology group study

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Background: Immune checkpoint inhibitors are effective for metastatic melanoma, but little is known about how is the efficacy and toxicity of this therapy in Turkish patients with metastatic melanoma. Here we present real-world efficacy and safety data of immune checkpoint inhibitors in Turkish patients with metastatic melanoma.

Methods: In this retrospective multi-institutional trial, patients with metastatic cutaneous melanoma who received immune checkpoint inhibitors between Jun 2013 and April 2021 were analyzed. Primary endpoints were objective response rate (ORR) and overall survival (OS). Secondary endpoints were progression free survival (PFS) and toxicity. For survival analysis, Log rank test and Cox regression analysis were used.

Results: 249 patients were included from 23 centers in Turkey for this trial. Median age was 59. 64% male, 28% BRAF mutant and 26% had brain metastases. 107 patients (43%) had metastasis at presentation (de novo metastasis). Overall, 173 (69%), 70 (28%) and 6 (3%) patients received Nivolumab, İpilimumab, and İpilimumab plus Nivolumab, respectively. At a median follow-up of 95 months, ORR of all patients was 37.7%. 28 patients (11.2%) had complete response, 66 patients (26.5%) had partial response and 29 patients (11.6%) had stable disease. Disease control rate was 49.3%. Median OS was 61 months (95% CI 47-74.9). Median PFS was 7 months (95% CI 5.9-8). On multivariate analysis, survival statistically favored patients without brain metastasis when compared to patients with brain metastasis ($p=0.003$) and patients with metastasis which occured after diagnosis when compared to patients with de novo metastasis ($p<0.001$). Grade 3-4 Immunotherapy-related adverse effects were reported in 38 patients (15.3%), more frequently represented by colitis, dermatitis, hypothyroidism and hypophysitis.

Conclusions: In this large real-life cohort showed that immune check point inhibitors were effective and prolonged survival of Turkish patients with metastatic melanoma. Also this trial demonstrated that brain metastasis and de novo metastasis were independent poor prognostic factors in Turkish patients with metastatic melanoma. irAE were mild and manageable.

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1077P Treatment outcomes in patients (pts) with melanoma brain metastases (MBM) undergoing systemic therapy: A systematic literature review (SLR) and meta-analysis (MA) of real-world evidence (RWE)

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Background: Immunotherapy (IO) and targeted therapy (TT) have revolutionized the treatment of pts with MBM, but clinical data on their efficacy are scarce. This analysis summarizes available RWE on the systemic treatment outcomes for pts with MBM.

Methods: An SLR of RWE for any systemic treatment in pts with MBM was conducted by searching Embase® and MEDLINE® databases from inception to February 23, 2020, and ASCO, AACR, ESMO, SMR, and EANO proceedings for 2018–2020. Records were screened by 2 investigators according to PICOS criteria. Records that reported OS outcomes on individual IO or TT therapies (with/without stereotactic radiosurgery [SRS]) were included in the MA. Kaplan–Meier (KM) curves for overall survival (OS) were digitized and converted to pseudo-individual pt data using the Guyot algorithm. MAs were performed by pooling KM curves and naive pooling of weighted median OS (mOS). For single-intervention studies, only reported values were used.

Results: A total of 57 publications (pertaining to 56 studies) were included for evidence synthesis. A total of 21 KM curves on 6 interventions and 1371 pts were digitized. mOS from pooled KM curves was numerically longer for nivolumab plus ipilimumab (NIVO + IPI; 20.6 mo; 95% CI, 17.0–22.9) versus other interventions (mOS ranging from 7.1–13.9 mo; table). Similar results were noted with the naive pooling method. Reporting on prior therapies, pt characteristics, and neurological symptoms was inconsistent.

Conclusions: RWE for MBM is scarce and heterogeneous; further research is warranted on optimal treatment for these pts. This SLR and MA suggest a clinical advantage with NIVO + IPI versus other systemic agents in pts with MBM. However, data interpretation is limited by evidence heterogeneity, inconsistent reporting, and small sample sizes. More consistent reporting of pt characteristics and outcomes is needed.

Table: 1077P MA results

Treatment	Pooled KM curves			Weighted estimates[a]		
	No. of KM curves	Pooled sample size, n	Median OS, mo (95% CI)	No. of cohorts	Pooled sample size, n	Median OS, mo
DAB	—	—	—	1	17	5.6[b]
DAB/DAB + TMB	1	132	9.5[a] (6.7—12.4)	1	132	9.5[b]
VMB	5	395	13.0 (10.9—13.9)	8	439	7.0
VMB + SRS	—	—	—	1	24	11.9[b]
IPI	5	105	7.1 (5.7—9.3)	5	134	6.4
IPI + SRS	7	143	13.9 (10.7—16.5)	3	72	15.2
IPI + SRS (after IPI)	—	—	—	1	14	6.4[b]
IPI + SRS (before/during IPI)	—	—	—	1	32	13.8[b]
NIVO + IPI	2	543	20.6 (17.0—22.9)	1	380	19.0[b]
NIVO	1	53	12.4[a] (6.2—NR)	1	53	12.4[b]

[a]Weighted by sample size. [b]As reported in original publication. CI, confidence interval; DAB, dabrafenib; IPI, ipilimumab; NIVO, nivolumab; NR not reached; TMB, trametinib; VMB, vemurafenib.

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1078P Real-world data on patients with melanoma brain metastases and outcome related to locoregional treatment modalities and systemic therapy

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Background: Novel medical therapies have revolutionized outcome for patients with melanoma. However, patients with melanoma brain metastases (MBM) still have a poor survival. Data are limited as these patients are generally excluded from clinical trials. Real-world data on changes in clinical outcome over time and efficacy data on treatment modalities could support more evidence-based treatment choices and determine overall benefit of modern therapies for patients with MBM.

Methods: Patients with MBM treated in the Capital Region of Denmark, between November 2008 and May 2020, were included retrospectively. Patient characteristics, treatment- and outcome data were collected from the Danish Metastatic Melanoma Database, pathology registries, electronic patient files and radiation plans. Targeted therapies and anti-PD1 antibodies were introduced in Denmark in 2015, and the cohort was split accordingly for comparison.

Results: A total of 527 patients with MBM were identified; 148 patients underwent surgical excision of MBM (14% surgery only), 167 patients had stereotactic radiosurgery (SRS) (14% SRS only), 270 patients whole brain radiation therapy (WBRT) (34% WBRT only) and 343 patients received systemic treatment (22% medical therapy only). The median overall survival (mOS) for patients diagnosed with MBM before and after 2015 was 4.5 and 7.4 months, respectively. For the entire cohort median intracranial progression free survival (icPFS) and mOS was 3.3 and 8.9 months for surgical excision, 3.1 and 7.1 months for SRS, 1.7 and 2.6 months for WBRT, and 4.2 and 6.6 months for 1st line systemic therapy after diagnosis of MBM. For patients treated with anti-PD1 plus anti-CTLA-4 12-months icPFS and OS was 48% and 54%, respectively, for anti-PD1 monotherapy 42% and 50%, and for BRAF/MEKi 11% and 33%. Of the 40 patients (7.6%) alive >3 years after diagnosis of MBM, 55% underwent surgical excision of MBM, 48% had SRS, 20% had WRBT and 80% received immunotherapy at some point after diagnosis.

Conclusions: Outcome for patients with MBM has significantly improved after 2015 but long-term survivors are rare. The majority of patients alive >3 years after diagnosis of MBM received immunotherapy.

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1079P Comparison of effectiveness and safety of nivolumab monotherapy or in combination therapy with ipilimumab in therapy-naïve and pretreated patients with advanced melanoma within the German noninterventional study NICO

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Background: Based on the first-line CheckMate 067 trial, nivolumab + ipilimumab (NIVO+IPI) has become a standard treatment in stage III/IV melanoma. However, limited data are available from prospective clinical trials on the effectiveness and tolerability of this combination in pretreated patients. Here, real-world data are presented especially for NIVO+IPI and also for NIVO in first and subsequent lines of therapy.

Methods: NICO is a prospective, observational, multicenter study in Germany associated with ADOREG. Enrolled patients with advanced melanoma begin treatment with NIVO or NIVO+IPI according to the marketing authorization. Patients are followed for up to 5 years. The primary objective is overall survival (OS) in patients receiving NIVO+IPI. Secondary objectives include OS in patients treated with NIVO, progression-free survival, safety profiles and adverse event management, treatment patterns, and patient-reported outcomes.

Results: To date (4th interim data cut, December 31, 2020), 762 patients with advanced melanoma have been enrolled; 486 patients received NIVO+IPI (62% in first-line, 34% in subsequent lines) and 276 patients received NIVO (74% first-line, 24% subsequent lines). Among pretreated patients, in both treatment arms approximately two-thirds had received 1 and around one-quarter had received 2 prior systemic therapies. In these pretreated patients, palliative radiotherapies were used 2—4 times more frequently at baseline compared with therapy-naïve patients (NIVO+IPI, 16.9% vs 3.7%; NIVO, 10.6% vs 4.4%). Objective response rates for NIVO+IPI and NIVO were similar in first (49% vs 50%) and subsequent (35% vs 36%) therapy lines. The corresponding median OS was superior for therapy-naïve patients (NIVO+IPI, 34.2 vs 11.2 months; NIVO, 31.1 vs 17.7 months). The general safety profiles of both immuno-oncology therapies were confirmed with no distinct treatment line—related differences.

Conclusions: Overall, both therapies, NIVO and NIVO+IPI, in first and subsequent therapy lines exhibit effective and safe treatment options for patients with advanced melanoma in routine care in Germany.

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1080P HORIZON: Final results from a 5-year ambispective study of 705 patients who initiated pembrolizumab for advanced melanoma in the French early access program

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Background: Based on early data, compassionate use of pembrolizumab (PEM) was granted to patients (pts) with advanced melanoma (unresectable or metastatic) in a French early access program (06/2014 − 09/2015). To explore real-world evidence (RWE), enrolment for this multicenter retro and prospective cohort study began in 06/2016. We present final results for effectiveness among this population.

Methods: Primary objective was 5 year (y) overall survival (OS) after PEM initiation. Other endpoints included yearly overall survival rates (OSR); real-world progression free survival (rwPFS; PEM initiation to progression); overall response rate (ORR, % of pts with complete or partial response [CR, PR]); disease control rate (DCR, % of pts with CR, PR or stable disease $\geq$ 24 weeks); duration of response (DoR; 1st objective tumor response until tumor progression or death) and long term safety data. Kaplan Meier survival analyses were used.

Results: Of 913 pts in the program, 705 pts (377 men) were enrolled in HORIZON with a mean delay of 1.2 y between diagnosis of advanced melanoma and 1st PEM infusion. Median follow up was 12.52 months (m; 95%CI [11.08; 15.87]), ranging from 0 to 70.1 m. At PEM initiation, mean age was 63.2 y, 52.1% had $\geq$ 3 metastatic sites and 71.3% were BRAF wild type. Only 179 pts (25.4%) were melanoma treatment (ttt) naïve, while 51.5% received prior ipilimumab. In this particularly severe population, OSR at 1 y to 5 y were 54.3%, 37.9%, 31.2%, 26.5% and 25.2%. At the 5 y follow up, median OS was 14.72 m (95%CI [12.2; 17.67]), rwPFS 3.21 m (95%CI [2.85 ; 3.64]). DoR was 30.07 m (95%CI [17.34; 43.41]), with 33.9% ORR and 42.4% DCR. Results will be presented by subgroups, including lines of ttt, presence of brain metastases, LDH levels, age and performance status.

Conclusions: Horizon is a large study, giving a real life long term landscape of non selected melanoma patients. Median OS and rwPFS are consistent with studies enrolling pts with prior therapy, the ORR and the 5Y OSR were respectively 33.9% and 25.2%. This is also a realistic estimation of the challenge to be filled by complementary therapeutic strategies in melanoma. We kindly thank all RIC-Mel network investigators.

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1081P Hospital variation in cancer treatments and survival outcomes of advanced melanoma patients: Nation-wide quality assurance in the Netherlands

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Background: The introduction of new systemic treatments for advanced melanoma has markedly changed the outcome of patients with metastatic melanoma. To assure high quality of care for patients treated in Dutch melanoma centers, hospital variation in treatment patterns and outcomes are evaluated in the Dutch Melanoma Treatment Registry. The aim of this study was to assess center variation in treatments and 2-year survival probabilities of patients diagnosed between 2013-2017 in the Netherlands.

Methods: We selected patients diagnosed between 2013-2017 with unresectable IIIC or stage IV melanoma, registered in the Dutch Melanoma Treatment Registry. Centers' performance on 2-year survival was evaluated using Empirical Bayes estimates calculated in a random-effects model with the use of new systemic therapies as a time-dependent covariate. Treatment patterns of the centers with the lowest and highest estimates for 2-year survival were compared.

Results: For patients diagnosed between 2014-2015, significant center variation in 2-year survival probabilities was observed even after correcting for case-mix and treatment with new systemic therapies. In the year with the largest variation (2014), between-center HRs ranged between 0.72-1.36 relative to the national average. Treatment patterns of the centers with the lowest estimates treated a higher percentage of patients with the anti-PD-1 antibodies (31% vs. 20%) and BRAF/MEK inhibitors (19% vs. 5%) in the first three lines of treatment compared to centers with higher estimates between 2013-2015. The differential use of new systemic therapies partially explained the observed variation. From 2016 onwards, no significant difference in 2-years survival was observed between centers.

Conclusions: Our data suggest that between 2014-2015, after correcting for patient case-mix, significant variation in 2-year survival probabilities between Dutch melanoma centers existed. A platform such as the Dutch Melanoma Treatment Registry, in which melanoma centers collaborate and have insight into variation in treatment patterns and outcomes between centers, results in fast implementation of new clinical developments across all Dutch melanoma centers.

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1082P Phase I study of ripretinib, a broad-spectrum KIT and PDGFRA inhibitor, in patients with KIT-mutated or KIT-amplified melanoma

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Background: Ripretinib, a kinase switch-control inhibitor designed to broadly inhibit *KIT* and *PDGFRA* mutations, is indicated in the treatment of adult patients (pts) with advanced gastrointestinal stromal tumor (GIST) who have received 3 or more prior tyrosine kinase inhibitors (TKIs), including imatinib. We present results of the *KIT*-altered (mutated or amplified) melanoma cohort in an ongoing phase I trial (NCT02571036). There are no approved TKIs for *KIT*-altered metastatic melanoma; ESMO and NCCN guidelines recommend specified KIT inhibitors as second-line therapy in certain situations; however, reported objective response rate (ORR) is typically $<$20% and progression-free survival (PFS) 3–4 months.

Methods: In the expansion arm of this phase I study, pts with *KIT*-altered melanoma were treated with ripretinib at the recommended phase II dose of 150 mg once daily (QD) (1 cycle every 28 days). Investigator-assessed responses were performed on Day 1 of Cycles 3, 5, 7, and every 3 cycles thereafter.

Results: As of February 12, 2021, of 26 pts enrolled with *KIT*-altered melanoma, 9 pts had mutations in exon 11, 4 in exon 13, 11 in exon 17, 1 in exon 18, and 1 had a *KIT* amplification. The median number of prior drug therapy lines was 2. Confirmed ORR was 23% (1 complete, 5 partial responses). Median PFS was 7.3 months, with a median duration of response of 7.4 months. Ripretinib and DP-5439 (active metabolite) plasma concentrations are generally consistent in pts with melanoma and those with GIST dosed at 150 mg QD, based on sparse pharmacokinetic sampling. The most common drug-related treatment-emergent adverse events (TEAEs; any grade) occurring in $>$15% of patients were increased lipase (n = 13), alopecia (n = 8), myalgia (n = 5), actinic keratosis, arthralgia, decreased appetite, fatigue, nausea, and palmar-plantar erythrodysesthesia syndrome (n = 4 each). The only drug-related Grade 3 TEAE occurring in $>$5% of patients was increased lipase (n = 8). There were no Grade $\geq$4 drug-related TEAEs.

Conclusions: Preliminary results show ripretinib had a manageable safety profile and demonstrated encouraging efficacy in *KIT*-altered melanoma with 23% ORR and 7.3 months mPFS, indicating that ripretinib may have a role in treating these pts.

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1083P A pilot study of engineered adenovirus ONCOS-102 in combination with pembrolizumab (pembro) in checkpoint inhibitor refractory advanced or unresectable melanoma

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Background: Patients (pts) with advanced melanoma resistant to immune checkpoint inhibitors (ICI) may benefit from oncolytic viruses. ONCOS-102 (Ad5/3-D24-GM-CSF), a chimeric oncolytic adenovirus expressing human granulocyte-macrophage colony stimulating factor, has demonstrated innate and adaptive immune responses in solid tumors. This study assessed the safety, clinical and immune responses of sequential (Part 1) or combined (Part 2) ONCOS-102 and pembro for pts with advanced melanoma after prior PD-1 blockade.

Methods: Pts received 3 doses of ONCOS-102 on days 1, 4, and 8 followed by up to 8 doses of pembro q3 weeks (Part 1, N=9) or 4 doses of ONCOS-102 on days 1, 4, 8, 15 followed by up to 8 doses of ONCOS-102 plus pembro q3 weeks (Part 2, N=12). Biopsies were done at baseline, week 3 and 9. Primary objective was safety; secondary objectives included Objective Response Rate (RECIST 1.1) and immunologic changes in tumor and peripheral blood.

Results: Safety (n=21) and efficacy (n=20) were assessed. Treatment emergent AEs included pyrexia (10%), chills (8%), nausea and hypertension (4%). There were no dose limiting toxicities. Best overall response was 7/20 (35%) (Part 1: 3/8 (38%); Part 2: 4/12 (33%)). Non-injected lesions decreased in 4 of 20 pts. ONCOS-102 increased CD8+ T-cells in both injected and non-injected tumors as well as in plasma. CD8+/Treg ratio increased in tumors of responding pts from day 22 to day 64. Numerous immune-related genes (cytotoxicity, co-stimulatory molecules, checkpoints, TLR9 and T cell inflammation) were upregulated in ONCOS-102 treated tumors.

Table: 1083P Patient characteristics

Parameters	Part 1 (n=8)	Part 2 (n=12)	Total (n=20)
Median age years (range)	73 (40-87)	72 (43-83)	73 (40-87)
Sex (F/M)	4/5	6/6	10/11
AJCC stage III/IV	6/2	5/7	11/9
Median tumor burden, mm (range)	37.5 (15-117)	73.5 (11.8-174)	55 (11.8-174)
Median time from last aPD1 failed treatment to study start, months (range)	1.8 (0.9-24.5)	1.9 (0.7-21.2)	1.9 (0.7-24.4)

Conclusions: Treatment with ONCOS-102 and pembrolizumab was well tolerated. Objective responses were seen in 35% of pts with PD-1 refractory melanoma, including in non-injected lesions. Immunologic changes in blood and tumor suggest ONCOS-102 may synergize with ICI.

Clinical trial identification: NCT03003676, 28/12/2016.

Legal entity responsible for the study: Targovax ASA.

Funding: Targovax ASA.

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1084P PLATForM: Descriptive analysis from a randomised, phase II study of novel spartalizumab combinations in previously treated unresectable/metastatic melanoma

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Background: Patients (pts) with advanced melanoma that progressed on immunotherapy/targeted therapy have an unmet medical need. Spartalizumab is an anti—PD-1 humanised monoclonal antibody (mAb) that may combine effectively with novel compounds to restore anti-tumour responses in PD-1—refractory disease. This is an analysis of a phase II, randomised, 2-part, multicentre, open-PLATforM (NCT03484923) study in pts with unresectable/metastatic melanoma progressing after prior anti—PD-1/L1 therapy.

Methods: The primary endpoint was overall response rate (ORR) per RECIST v1.1; secondary endpoints included duration of response and biomarker assessments. The selection phase comprised 4 Arms combining spartalizumab with ieramilimab (anti-LAG3 mAb; Arm 1), capmatinib (Arm 2), canakinumab (Arm 3) or ribociclib (Arm 4). An adaptive design during the selection phase allowed dropping arms for futility, adding new arms, and selecting arm(s) for expansion. Bayesian methodology was used for futility and efficacy assessments at each interim analysis (IA).

Results: As of 1 Feb 2021, 175 pts were randomised; 45, 43, 43, and 44 pts in Arms 1-4, respectively. Median age was 59 y, and 57% received ≥2 prior therapies. Overall, 166/175 pts discontinued treatment, primarily due to progressive disease (65%). ORRs in Arms 1-4 were 7% (n = 3/45), 5% (2/43), 5% (2/43) and 7% (3/44), respectively. All arms crossed the specific futility probability threshold and were declared futile at previous IAs. In Arm 1, 6 pts had LAG-3+ melanoma at baseline (≥5% + tumour cells by IHC), of which 2 pts had a partial response, both ongoing for ≈23 months. Overall, grade ≥3 adverse events occurred in 59% of pts (53%, 51%, 36%, 93% in Arms 1-4, respectively). There were 14 on-treatment deaths; 5/45 in Arm 1, primarily due to melanoma progression (4/45).

Conclusions: Although all tested combinations have been declared futile, Arm 1 data suggest pts with LAG-3+ melanoma may be more likely to respond to spartalizumab + ieramilimab treatment. Consequently, Arm 1A (spartalizumab + ieramilimab) was opened and is currently recruiting pts with previously treated unresectable/metastatic LAG-3+ melanoma.

Clinical trial identification: NCT03484923.

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1085P Ph I/II study of PI3K-β inhibitor GSK2636771 (G771) in combination with pembrolizumab (P) in patients (pts) with PTEN loss and melanoma or other advanced solid tumors

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Background: Immune checkpoint blockade (ICB) improves survival in metastatic melanoma (MM), but many pts progress or recur and ultimately die from this disease. PTEN loss, which occurs in up to 30% of MM pts, activates the PI3K-AKT pathway and correlates with decreased tumor infiltrating lymphocytes (TIL) and lower response rate (RR) to ICB. In preclinical models of PTEN-null melanoma selective inhibition of PI3Kβ with G771 combined with ICB increased CD4+/8+ TIL and survival. Thus, we conducted a phase I/II study (NCT01458067) of PI3Kβi + P in pts w/ PTEN loss, including PD-1 refractory MM.

Methods: Ph I primary objective (obj) was determining the Recommended Phase II Dose (RP2D) of G771 + P (3+3 design). P was given at 200 mg IV and dose escalation started at 300mg PO qd of G771 for 21 days. Ph II primary objs were safety, tolerability, and RR by RECIST 1.1. Secondary obj included PKs of the G771 and PD effects in tumor and blood. MM pts must have progressed on PD1 or not achieved response after 6 mos of therapy. PD1-naïve pts with advanced prostate, triple-negative breast (TNBC), colorectal or endometrial cancer were also eligible. PTEN loss was defined by mutation or loss of protein expression by IHC.

Results: Ten pts were accrued to the dose escalation phase (300mg and 400mg), but RP2D was set at 200 mg of G771 due to a DLT of acute kidney injury and data from other ongoing studies. A total of 27 pts (of 41 planned) were treated: 10 MM, 12 prostate, 2 TNBC, 1 each of endometrial, lung, colon. Study accrual stopped due to sponsor decision to cease development of G771. PRs were achieved in 3 pts (12%) and clinical benefit rate (CR/PR/SD) was 52%, including 3 pts with >1 yr on therapy. Median PFS was 3.4 mos (95% CI: 2.5-6.0). 44% pts experienced gr 3/4 toxicities, 3 pts discontinued due to toxicity. Paired biopsies were obtained when safe/feasible; RR and translational studies will be presented at the conference.

Conclusions: G771 (200 mg PO QD) + P was tolerable, but response was modest. Translational studies will be critical to understanding mechanisms of response and resistance to G771 + P and to develop additional strategies to overcome resistance to ICB due to PTEN loss.

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1086P IBI310 alone or in combination with sintilimab for advanced melanoma: Updated results of a phase Ia/Ib study

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Background: The combination of PD-1 and CTLA-4 blockades showed improved antitumor activities in advanced melanoma. But most data derived from cutaneous subtype and less is known about acral and mucosal patients in East Asia. The study reported updated results of a phase Ia/Ib study that evaluated IBI310 (CTLA-4 inhibitor) alone or plus sintilimab (PD-1 inhibitor) in advanced melanoma including acral and mucosal subjects.

Methods: This was a two-part study. Part A was IBI310 monotherapy setting, and part B was IBI310—sintilimab combination setting. In part A, patients (pts) were treated with IBI310 (IV Q3W) at the doses of 0.3 mg/kg, 1, 2 or 3 mg/kg, for up to 3 cycles (after 28-day DLT evaluation) followed by IBI310 (IV Q12W) if appropriate. In part B, pts with advanced melanoma were treated with IBI310 at the doses of 1, 2 or 3 mg/kg, plus sintilimab at a fixed dose of 200 mg (IV Q3W) for 4 cycles, followed by sintilimab maintenance therapy. The primary endpoint was safety in the two parts and the second endpoints were objective response rate (ORR) and disease control rate (DCR) of the combination therapy.

Results: As of April 14, 2021, 10 and 34 melanoma pts were enrolled in part A and part B, respectively. In part B, there were 3, 31 pts at stage III, IV; 10, 7, 17 pts with 0, 1, ≥2 prior lines of treatments; 24, 9, 1 pts with LDH≤ ULN, > ULN&≤2 x ULN, >2 x ULN respectively. There were no DLTs in the two parts. In part A, only one treatment-related AE (TRAE) of grade 3 (gamma glutamyltransferase increased) was reported; the most commonly reported TRAEs was pruritus (40%). In part B, any grade TRAEs reported in 91.2% of 34 pts, and most were grade 1-2; ≥grade 3 TRAE occurred in 20.6% of 34 pts. No pts experienced Grade 5 TRAE. Among 34 pts in part B, 8 pts obtained complete response (CR) or partial response (PR); the ORR was 23.5% (95% CI: 10.7, 41.2), and DCR was 50.0% (95% CI: 32.4, 67.6). There were 4 SD with decreased target lesions. The ORR were 33.3%, 27.8%, 20.0% for acral, NCSD, and mucosal pts respectively. For pts with 0, ≥1 prior lines of treatments, the ORR were 30% and 20.8% respectively. The part B is ongoing.

Conclusions: IBI310 monotherapy or plus sintilimab were well-tolerated in advanced melanoma. IBI310—sintilimab combination showed a preliminary response benefit in advanced melanoma.

Clinical trial identification: NCT03545971.

Legal entity responsible for the study: The authors.

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1087P The importance of anti-PD-1 dosing in the treatment of patients with inoperable or metastatic melanoma

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Background: Anti-programmed cell death-1 antibodies (anti-PD-1) has become a standard treatment option for melanoma patients. Unfortunately, there are no clinical data on the efficacy of anti-PD-1 at fixed-doses in routine practice.

Methods: Consecutive patients treated with nivolumab (N) or pembrolizumab (P) for inoperable and metastatic melanoma in comprehensive cancer centers between 2016 and 2020 were enrolled in the study. The initial anti-PD-1 dose in mg/kg was calculated in patients. Baseline factors together with the initial dose anti-PD-1 were evaluated to identify predictors of progression-free (PFS) and overall (OS) survival. PFS and OS were assessed using Kaplan—Meier and Cox models. The Chi Square statistic was used for testing relationships between categorical variables.

Results: Overall, 1053 patients were included in the present analysis (N=590, P=463). In N group there were no differences in OS and PFS between the group 240 mg Q2W vs. 480 mg Q4W and in OS between the group that received the first dose of N $\leq$ 3 vs. $>$ 3 mg/kg or treatment Q2W vs. Q4W. However, in univariate analysis there were statistically significant differences in PFS between the group that received the first dose of N $\leq$ 3 vs. $>$ 3 mg/kg (p=0.0002, HR=1.6, CI 95% 1.2-2.0) or treatment Q2W vs. Q4W (p=0.0023, HR=1.4, CI 95% 1.1-1.8), this was not confirmed in the multivariate analysis. The first dose of N $<$ 3 vs. $\geq$ 3mg/kg correlated with response to treatment (RR) and disease control rate (DCR) (p=0.03 and p=0.0132, respectively) but not correlated with the occurrence of immune related adverse events (irAEs). Treatment Q2W vs. Q4W and 240 mg Q2W vs. 480 mg Q4W were not correlated with RR and DCR, however there were correlated with the occurrence of irAE (p=0.0025 and p=0.0047, respectively). In P group there were no significant differences in OS and PFS between the group that received the first dose of P $\leq$ 2 and $>$2 mg/kg, treatment Q3W vs. Q6W and 200 mg Q3W vs. 400 mg Q6W. There were also no correlation with RR and DCR however, there was correlation with the occurrence of irAEs.

Conclusions: Anti-PD-1 dosing had no effect on OS and PFS in the study population. However, a correlation of dosing with the occurrence of irAE was demonstrated, but this requires confirmation in further studies.

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1088P Adjuvant dabrafenib plus trametinib (DT) treatment completion in patients with resected melanoma in Spain: A retrospective observational study (GEM 1901 - DESCRIBE-AD)

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Background: DT combination has shown efficacy in the adjuvant setting for BRAF mutated melanoma (BMM) patients (pts) in clinical trials. However, 26% of pts discontinued treatment (tt) due to unacceptable toxicity. DESCRIBE-AD study aims to collect real-world evidence on the discontinuation of adjuvant DT in Spain.

Methods: An observational retrospective study was carried out in 23 GEM sites in Spain. Histologically confirmed and resected BMM pts previously treated with DT in the adjuvant setting were included. Only surgical resection was allowed as a prior tt to DT. DT discontinuation rate and time to treatment discontinuation was the primary objective. Secondary objectives included safety and efficacy of the combination.

Results: From 10/2020 to 03/2021, 65 pts were included. Median age was 58y, 55% were male and 60%/25%/14% had an ECOG PS 0/1/Uk respectively. Allocation of stage IIIA, IIIB and IIIC according to TNM AJCC 7th edition was 26%, 22% and 28%, respectively. Ulceration was present in 40%, Breslow $\geq$2 mm in 71%, and nodes were microscopically and macroscopically affected in 39% and 22% of pts, respectively. DT discontinuation rate due to treatment-related adverse events (TRAEs) of any grade happened in 6 pts (9%). Other discontinuation reasons included patient's decision (6%), physician decision (6%), DT unrelated AEs (3%), PD (5%) and other (5%). The median time to DT discontinuation was 9 m (95%CI: 5-11). 76.9% of pts presented at least 1 TRAE. Most frequent grade $\geq$3 TRAEs were pyrexia (3%), asthenia (3%) and diarrhea (3%). Unscheduled hospitalizations and extra clinical tests occurred in 4 (6%) and 14 (22%) pts respectively. After a median follow up of 20 m (95%CI: 18-22), 6 pts (9%) were exitus due to disease progression, with a 12-month overall survival rate of 100%.

Conclusions: TRAEs and DT discontinuation rate in our study were less frequent than previously reported in clinical trials. DT proved effectiveness during treatment and a manageable toxicity profile in the real world that did not differ from previous reports in clinical trials and led to low incidence of unscheduled medical visits and tests.

Legal entity responsible for the study: Grupo Español Multidisciplinar de Melanoma (GEM).

Funding: Novartis.

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1089TiP Efficacy and tolerability of anti-PD1 antibody in combination with pulsed hedgehog inhibitor in advanced basal cell carcinoma

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Background: Basal cell carcinoma (BCC) is the most common skin cancer. Main drivers of BCC development are mutations in the hedgehog (HH) pathway, which allow proliferation of the malignant cells leading to tumor formation. Interestingly, despite carrying a high tumor mutational burden, BCC shows none or little immune infiltration and is considered an "immune-privileged" tumor. Most BCCs can be treated with local therapies, such as surgery, topical medications, cryo-, photodynamic or radiotherapy, but in advanced BCCs, systemic therapy is needed. HH pathway inhibitors (HHI) are small molecules, inhibiting the downstream signalling and eliciting anticancer effects. HHI cause clinical response in HH pathway-dependent tumours and are widely used in management of BCC. However, a subset of patients develops primary or secondary resistance, which leads to disease progression. HHI increase CD8+ T cell infiltration in BCC, indicating a change in immune susceptibility of the tumor. This suggests a synergistic effect of combination of HHI with an immunotherapeutic agent. We initiated a clinical trial to evaluate tumor response and induction of immune response in patients with advanced BCC treated with a combination of Cemiplimab (anti-PD1 antibody) and Sonidegib (hedgehog inhibitor).

Trial design: 20 patients with advanced BCC will be included in this open label, non-randomized clinical trial. After a run-in phase with Sonidegib, patients will receive a combination therapy of Cemiplimab and pulsed dosing Sonidegib (2 weeks on 2 weeks off). Primary endpoint of the trial is best response at any time between treatment start and 26 weeks after the initiation of the treatment. Secondary endpoints are tumor response at 26 weeks, changes in histology and immunogenicity of the tumor and treatment safety. Response will be evaluated according to immune related response criteria (irRC). Safety will be assessed using CTCAE v5. Tumor immunogenicity will be assessed in patients with biopsy assessable tumors and will include cellular and molecular markers, including programmed cell death ligand 1, HLA I and II, and lymphocyte infiltration. Additionally, optional fine needle aspirations will be performed during each visit.

Clinical trial identification: NCT04679480.

Legal entity responsible for the study: The authors.

Funding: Sanofi, SunPharma.

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1090TiP A phase II, open label, multicenter study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with treatment-naïve metastatic Merkel cell carcinoma: The MERKLIN 1 study

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Background: Merkel cell carcinoma (MCC) is a rare and highly aggressive human skin cancer often caused by the Merkel cell polyomavirus or extended exposure to sunlight. Since the approvals of avelumab globally and subsequently pembrolizumab (US only), anti-PD-(L)1 antibody therapies have become standard of care for MCC patients in recent years. Despite these successes, a significant proportion of MCC patients do not respond or relapse on such monotherapy and have an unmet medical need for a more effective first-line therapy. Preclinical data suggest that the small molecule selective class I histone deacetylase inhibitor (HDACi) domatinostat addresses critical, well-described escape mechanisms of MCC. These escape mechanisms include the epigenetic downregulation of the antigen processing and presentation machinery leading to an insufficient recognition of tumor cells by the immune system. Treatment with domatinostat is hypothesized to favorably modulate the tumor environment and synergize with anti-PD-L1 therapy for a higher response rate, deeper responses, and longer duration of response.

Trial design: MERKLIN 1 (NCT04874831) is a phase II, multicenter, single arm clinical trial of the orally administered HDACi domatinostat in combination with the anti-PD-L1 antibody avelumab for patients with treatment-naïve metastatic MCC. A total of 100 patients will be enrolled in up to 40 clinical study sites initially in Europe. The primary objective is to evaluate the clinical efficacy of the combination in treatment-naïve metastatic or distally recurrent MCC patients as determined by the objective response rate, defined as the percentage of patients having a confirmed complete response or partial response according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) by independent review. Secondary objectives include additional efficacy assessments, safety, health related quality of life and

pharmacokinetics of domatinostat and avelumab. Correlative aims include evaluating biomarkers for association with clinical benefit.

Clinical trial identification: 4SC-202-4-2019 (Protocol Number), EudraCT 2019-003575-19.

Legal entity responsible for the study: 4SC AG, collaborator Merck KG.

Funding: 4SC AG.

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1091TiP STARBOARD: Randomized phase III study of encorafenib (enco) + binimetinib (bini) + pembrolizumab (pembro) for first-line treatment of metastatic or unresectable locally advanced BRAF V600-mutant melanoma

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Background: Approximately 50% of patients (pts) with metastatic melanoma have *BRAF* V600 mutations, which promote melanoma progression through constitutive activation of the MAPK pathway. Current treatment recommendations for metastatic or unresectable *BRAF* V600-mutant melanoma include BRAF inhibitors (BRAFi) + MEK inhibitors (MEKi) (eg, enco + bini) and immune checkpoint inhibitors (CPIs; eg, pembro). BRAFi and MEKi may increase the sensitivity of *BRAF* V600-mutant tumors to CPIs. STARBOARD aims to compare the efficacy, safety, and tolerability of first-line enco + bini + pembro vs pembro alone for the treatment of metastatic or unresectable locally advanced *BRAF* V600-mutant melanoma.

Trial design: STARBOARD is a randomized, double-blind, placebo-controlled, phase III study with a safety lead-in (SLI). Approximately 24 and 600 pts will be enrolled into the SLI and phase III study, respectively; phase III randomization will be stratified by prior systemic adjuvant treatment and disease stage. Pts must have histologically confirmed metastatic or unresectable cutaneous melanoma (AJCC 8th ed.) with *BRAF* V600E/K mutation (by local laboratory assay); measurable disease (RECIST v1.1); ECOG performance status 0 or 1; and adequate bone marrow, hepatic, and renal function. Pts must not have received prior first-line systemic therapy. Prior adjuvant treatment with BRAFi and/or MEKi or anti—PD-1 or anti—CTLA-4 is permitted. Pts with prior or current symptomatic brain metastases will be excluded except those with $\leq$ 3 brain lesions (either previously treated, asymptomatic, and stable for $\geq$ 28 days prior to enrolment; or untreated, asymptomatic, and each $<$ 5 mm). Study treatments and endpoints are shown in the table. Enrolment began on 11 February 2021.

Table: 1091TiP

	SLI	Phase III
Treatment (21-day cycle)	**Enco 450:** enco 450 mg QD + bini 45 mg BID + pembro 200 mg IV Q3W or **Enco 300:** enco 300 mg QD + bini 45 mg BID + pembro 200 mg IV Q3W	**Triplet:** per SLI, enco 450 or 300 **Control:** placebo + pembro 200 mg IV Q3W
Endpoints		
Primary	DLTs	PFS
Secondary	AEs, ORR, DCR, TTR, PK	**Key:** OS (triplet vs control) **Other**: PFS, ORR, DOR, DCR, TTR, PFS2, QOL, AEs, PK
Tertiary	Time to onset of brain metastases; biomarkers	

AE, adverse event; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, PFS after next line of therapy; PK, pharmacokinetics; QOL, quality of life; TTR, time to response.

Clinical trial identification: NCT04657991.

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Disclosure: D. 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1092TiP Investigational (Inv) agents with or without pembrolizumab (pembro) or pembro alone in melanoma (mel): KEYMAKER-U02

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Background: Pembro is a SOC for unresectable or metastatic mel and adjuvant treatment (tx) of stage III mel. There is need to improve outcomes in patients (pts) with advanced mel and brain metastases (BM) and to reduce tumor burden before surgery.

Trial design: KEYMAKER-U02 is a phase I/II, rolling arm, multicenter, open-label, adaptive design study of Inv agents ± pembro or pembro alone in mel. Recruitment is ongoing in 4 substudies. Substudy 02A: Pts with unresectable stage III/IV PD-1—refractory mel (disease progression after ≥2 doses of anti—PD-1/PD-L1 therapy) will be randomized equally to tx arms with ≥1 Inv agent(s) ± pembro. Planned enrollment is ∼100 pts/arm. Substudy 02B: Pts with unresectable tx-naive stage III/IV mel will be randomized 2:1 to combination of ≥1 Inv agent(s) ± pembro or pembro alone stratified by baseline LDH status (normal/elevated) and prior adjuvant anti—PD-1 therapy (yes/no). Planned enrollment is ∼90 pts in the combination arms, ∼45 in the pembro arm. Substudy 02C: Pts with stage IIIB/IIIC/IIID mel who are eligible for neoadjuvant therapy will be randomized to combination of ≥1 Inv agent(s) ± pembro or pembro alone. Surgical resection will occur 6 weeks after the first dose of neoadjuvant tx. Planned enrollment is ∼25 pts in the combination arms, ∼15 in the pembro arm. Substudy 02D: Pts with stage IV mel who have ≥1 and ≤5 measurable BM by RECIST v1.1, confirmed by blinded independent central review (BICR), no neurologic symptoms of BM, and who have not received >3 lines of prior tx are eligible. Pts will be included in PD-1—naive or PD-1—exposed cohorts and randomized to combination arms of ≥1 Inv agent(s) with pembro. Planned enrollment is ∼50 pts (≤100 for PD-1—naive cohort) per each Inv agent arm. Tx will continue for ≤2 y in substudies 02A, 02B, and 02D, and ≤1 y in 02C. Primary end points are safety for all substudies; ORR by BICR per RECIST v1.1 for substudies 02A, 02B, and 02D; and pathological CR (pCR) by central review for substudy 02C. Secondary end points are DOR for substudies 02A and 02B; recurrence-free survival, near pCR, and pathological PR rate for substudy 02C; and DOR, PFS, BM response rate per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM), and BM-DOR per RANO-BM for substudy 02D.

Clinical trial identification: NCT, first posted NCT04305041 (substudy 02A), March 12, 2020 NCT04305054 (substudy 02B), March 12, 2020 NCT04303169 (substudy 02C), March 10, 2020 NCT04700072 (substudy 02d), January 7, 2021.

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1093TiP An open-label, multicenter, phase I/II clinical trial of RP1 as a single agent and in combination with nivolumab in patients with solid tumors [IGNYTE]

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Background: RP1 is an enhanced potency oncolytic HSV-1 which expresses a fusogenic glycoprotein (GALV-GP R-) and granulocyte macrophage colony stimulating factor (GM-CSF). Pre-clinical studies with RP1 demonstrated potent GALV-GP R-enhanced anti-tumor activity and immunogenic cell death. This phase I/II (Ph I/II) study (NCT03767348) was designed to evaluate the safety and efficacy of RP1 as single agent and in combination with nivolumab (nivo) in pts with advanced solid tumors, including pts whose disease failed prior anti-PD1/PD-L1 therapy.

Trial design: This is a multi-center, first-in-human, open label, non-randomized Ph 1/2 study of RP1 alone and in combination with nivo in pts with advanced solid tumors, including those that failed prior anti-PD1/PD-L1 therapy. The Ph 1 dose escalation and expansion are fully enrolled. Approximately 260 pts are expected to be enrolled in the ongoing Ph 2 portion across five cohorts; melanoma (n=30, enrolment complete), non-melanoma skin cancer (n=45, to include 15 pts with anti-PD1/PD-L1 failed disease), MSI-H/dMMR (n=30), anti-PD1/PD-L1-failed non-small-cell lung cancer (n=30) and anti-PD1 failed cutaneous melanoma (n=125). Pts in the Ph 2 portion receive up to 10 mL of RP1 intratumorally into one or more deep/visceral and/or superficial lesions at the recommended Ph 2 dose ($1x10^6$ PFU/mL × 1 followed by $1x10^7$ PFU/mL × 7). Following the first dose of RP1, nivo (240 mg IV Q2W for 4 months then 480 mg IV Q4W for up to 2 years) is subsequently administered in combination. Pts may receive up to 8 additional doses of RP1 if they meet protocol-specified criteria. Tumor assessments are performed Q8W. The primary objectives of the Ph 2 part of the study are to assess the safety, tolerability, and overall response rate (ORR) of RP1 in combination with nivo. Secondary objectives include duration of response, complete response rate, disease control rate, and PFS. Exploratory objectives include biodistribution and shedding analysis of RP1 and biomarker studies, including analyses of pre- and on-treatment tumor biopsies and blood samples. Enrollment is currently ongoing in the UK and US, with additional sites in the EU expected to open in 2021.

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Legal entity responsible for the study: Replimune Group Inc.

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1094TiP A randomized, controlled, open-label, phase II study of cemiplimab as a single agent and in combination with RP1 in patients with advanced cutaneous squamous cell carcinoma [CERPASS]

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Background: Prognosis of advanced and metastatic cutaneous squamous cell carcinoma (CSCC) remains dismal. The anti-PD1 antibody cemiplimab was the first agent approved for the treatment of advanced CSCC. 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. In preliminary study, high response rates including complete response have been observed in patients with CSCC treated with RP1 combined with nivolumab. The objective of this trial is to evaluate the safety and efficacy of RP1 + cemiplimab versus cemiplimab alone in advanced CSCC (NCT04050436).

Trial design: This global, multicenter, randomized phase II study is enrolling patients (pts) with metastatic CSCC or with unresectable, locally advanced CSCC who are not candidates for/refuse surgery or radiotherapy. Key eligibility criteria include no prior treatment with anti-PD1/PD-L1 antibodies or oncolytic viruses. The clinical trial will enroll approximately 180 pts at approximately 75 centers in the EU, Australia, Canada and USA. Pts will be randomized in a 2:1 ratio favoring the RP1 + cemiplimab arm. Pts will receive 350 mg of cemiplimab intravenously (IV) Q3W for up to 108 weeks. In the RP1 + cemiplimab arm, RP1 will be 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 cemiplimab. Pts in the combination arm may receive up to 8 additional RP1 doses. No crossover will be allowed. Pts will be stratified by disease status and prior systemic therapy. Tumor assessments will be performed every 9 weeks. Primary endpoints are overall response rate and complete response rate by blinded central review. Secondary endpoints include safety, progression free survival, duration of response and overall survival. Exploratory endpoints include viral shedding and biodistribution, and immune biomarker analyses. This trial is currently enrolling pts.

Clinical trial identification: NCT04050436.

Legal entity responsible for the study: Replimune Group Inc.

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1095TiP Daromun, a dermato-oncology drug in development for stage III and IV melanoma and non-melanoma skin cancers: A clinical overview

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Background: Daromun (Nidlegy®) is an immuno-oncology drug in clinical development for the treatment of melanoma and non-melanoma skin cancers (NMSC). The product, which is administered intralesionally, consists of two antibody-cytokine fusions as active principles (L19IL2 and L19TNF), which act synergistically to directly kill tumor cells while also inducing a systemic anti-tumor immune response. The drug is the first oncology product to receive EMA's agreement for development as combination pack. Daromun is being investigated in two phase III studies in the neoadjuvant setting for fully resectable, locally advanced melanoma in EU and in the US. A phase II study in locally advanced NMSC (BCC and cSCC) has recently started in Europe. Finally, a phase II study in patients with unresectable melanoma, relapsed after or refractory to anti-PD1 treatment, is about to start in the US.

Trial design: The phase III neoadjuvant (NCT02938299 and NCT03567889) open label, randomized, controlled trials feature treatment with Daromun (13 Mio IU L19IL2 and 400 µg L19TNF) q1W over 4 weeks, followed by surgery and evtl. adjuvants decided by the treating physician (exptl. Arm). Patients randomized to the control arm receive the standard of care (surgery + adjuvants). Primary endpoint is RFS, secondary

endpoints include OS, pathologic responses, safety. The EU study, ongoing at 20 centers in four countries, has enrolled more that $^{3}/_{4}$ of the expected sample size and has already passed the two interim analyses foreseen by the protocol, with the DSMB recommending prosecution of the study. The US trial has started later, is running at 5 clinical centers, while more centers are in the process of being opened. A phase II, open label study (NCT04362722) in 40 patients with localized, injectable BCC or cSCC is ongoing in Switzerland and expansion in other EU countries is planned. Patients receive L19IL2/L19TNF injections (6.5 Mio IU and 200 µg/dose, respectively) q1W over 4 weeks. Primary endpoint is ORR (CR + PR) at week 6 (RECIST 1.1). Encouraging results have been observed in the first treated patients. Finally a phase II, 3-arms controlled study in unresectable advanced melanoma patients resistant to anti-PD1 inhibitors is expected to start in q3 2021 in the US.

Clinical trial identification: NCT02938299, NCT03567889, NCT04362722.

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