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1076O Adjuvant nivolumab (NIVO) vs ipilimumab (IPI) in resected stage III/IV melanoma: 4-y recurrence-free and overall survival (OS) results from CheckMate 238

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Background: NIVO has shown improved recurrence-free survival (RFS) vs IPI in patients (pts) with resected stage III/IV melanoma in the phase III CheckMate 238 study. Updated 48-mo RFS and distant metastases-free survival (DMFS) and primary OS are presented.

Methods: Pts aged ≥ 15 y with completely resected stage IIIB/C or IV melanoma were stratified by stage and tumor programmed death ligand 1 (PD-L1) status and randomized 1:1 to NIVO (3 mg/kg Q2W; n = 453) or IPI (10 mg/kg Q3W for 4 doses, Q12W thereafter; n = 453) for ≤ 1 y or until disease recurrence/unacceptable toxicity. The primary endpoint was RFS. Secondary endpoints included OS and safety; DMFS in stage III disease was exploratory.

Results: At 48 mo of follow-up, NIVO continued to demonstrate superior RFS vs IPI (HR 0.71; 95% CI 0.60–0.86; $P = 0.0003$; Table). DMFS in pts with stage III disease favored NIVO (HR 0.79; 95% CI 0.63–0.99). At 48 mo, the number of OS events (n = 211) was lower than anticipated (n = 302) and OS rates were comparable: 78% (95% CI 73.7–81.5) with NIVO and 77% (95% CI 72.2–80.3) with IPI (HR 0.87, 95.03% CI 0.66–1.14, $P = 0.3148$). Subsequent systemic next-line therapy was received by 150 (33%) NIVO-treated pts and 189 (42%) IPI-treated pts; more IPI-treated pts (34% vs 23%) received subsequent systemic immunotherapy (IO). Any-grade late-emergent treatment-related adverse events (TRAEs; reported > 100 d after last dose) were observed in 18 (4%) NIVO-treated pts and 25 (6%) IPI-treated pts, with grade 3/4 in 3 (1%) and 7 (2%), respectively.

Table: 1076O

	RFS	DMFS	OS
ITT population[a]	0.71 (0.60–0.86)	0.79 (0.63–0.99)	0.87 (0.66–1.14)[b]
Stage[c]			
IIIB	0.70 (0.50–0.98)	0.78 (0.54–1.14)	0.88 (0.53–1.47)
IIIC	0.74 (0.57–0.96)	0.82 (0.62–1.09)	0.96 (0.67–1.39)
IV	0.74 (0.49–1.11)	-	0.72 (0.38–1.38)
PD-L1			
≥ 1%	0.68 (0.54–0.86)	0.77 (0.58–1.04)	0.73 (0.51–1.04)
< 1%/ind	0.76 (0.57–1.02)	0.80 (0.56–1.14)	1.09 (0.72–1.67)
≥ 5%	0.67 (0.47–0.96)	0.79 (0.51–1.22)	0.74 (0.43–1.27)
< 5%/ind	0.74 (0.59–0.91)	0.80 (0.61–1.04)	0.92 (0.68–1.26)
BRAF			
Mutant	0.79 (0.60–1.05)	0.82 (0.57–1.16)	1.13 (0.73–1.74)
Wild-type	0.69 (0.53–0.91)	0.79 (0.57–1.09)	0.76 (0.51–1.12)

Data are HR (95% CI) for NIVO vs IPI; [a]Stratified; [b]95.03% CI; [c]AJCC 7th ed.; Ind, indeterminate.

Conclusions: NIVO continued to demonstrate improved RFS and DMFS vs IPI at 48 mo in pts with stage III/IV melanoma at high risk of recurrence. OS events (n = 211) were lower than anticipated (n = 302). OS rates were similar to NIVO and IPI, although use of subsequent IO therapy was higher in the IPI arm. Late-emergent TRAEs were consistent with the established safety profile of NIVO and IPI, with more events reported with IPI.

Clinical trial identification: NCT02388906.

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1077MO PD1 blockade with pembrolizumab in classic and endemic Kaposi sarcoma: A multicenter phase II study

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Background: While the treatment of iatrogenic and HIV-related KS is well defined, mostly based on restoring the immune function, the treatment of classic/endemic KS is less codified. Chemotherapy or interferon are used for patients (pts) with extensive cutaneous and/or visceral KS but the tolerance may be poor in elderly pts, and long-term remissions are rare. Major efficacy of PD1 blockade has been demonstrated in Merkel cell carcinoma, another virus-induced tumor, in part driven by the immunogenicity of virus-associated antigens. Because of the involvement of HHV8 in KS and their good tolerance in older pts, the use of anti-PD1 appeared as a promising tool for classic/endemic KS.

Methods: We conducted a multicenter single arm phase II trial in pts with classic/endemic KS with cutaneous extension requiring systemic treatment. Pts were treated with pembrolizumab (pembro) 200mg every 3 weeks for 6 months. Tumor assessment was performed by physical examination at each cycle (count, size, nodularity and color of target cutaneous lesions). The primary endpoint was the best overall response rate (BORR, ACTG criteria). A tumor response probability >30% using the Simon's 2 stage optimal design was required to conclude that the drug was active.

Results: 17 pts (47% with classic and 53% with endemic KS) were included. 6 pts (35%) had lymph node extension. 12 pts (71%) were previously treated with chemotherapy. Median follow up was 25 weeks. Two pts had CR, 10 PR and 4 SD as best response (1 still on treatment; threshold of drug activity achieved). One pt discontinued treatment for toxicity. Treatment-related adverse events occurred in 11 pts (65%), including 1 grade 3 (6% - acute reversible cardiac decompensation). On baseline tumor samples, the lack of PDL1 expression on tumor and immune cells was associated with poor efficacy of pembro. The germline HLA-1 evolutionary divergence (HED) was determined for 16 pts. The 4 pts with SD as best response had significantly lower HED for HLA-B than pts with PR or CR.

Conclusions: In the first prospective trial assessing the role of PD1 blockade in classic/endemic KS, pembro showed efficacy with 12 out of 16 of pts having CR or PR (BORR above 30%) and had an acceptable safety profile. If confirmed, this treatment could rapidly become standard of care.

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1078MO MIND-DC: A randomized phase III trial to assess the efficacy of adjuvant dendritic cell vaccination in comparison to placebo in stage IIIB and IIIC melanoma patients

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Background: Dendritic cells (DCs) are highly specialized antigen-presenting cells which are essential for the activation of immune responses. Autologous DCs, directly isolated from peripheral blood, loaded with tumor antigens and matured in vitro, can induce tumor-specific immune responses and clinical responses in cancer patients.

Methods: In this phase III clinical trial, patients with resected stage IIIB or IIIC cutaneous melanoma (AJCC 7th edition) were randomized in a 2:1 ratio to adjuvant treatment with DC vaccination or placebo. The active treatment arm consisted of intranodal injections with autologous CD1c+ myeloid DCs and plasmacytoid DCs loaded with tumor antigens (gp100, tyrosinase, MAGE-C2, MAGE-A3 and NY-ESO-1). When adjuvant treatment with anti-PD1 antibodies became available in the Netherlands in November 2018, accrual was stopped prematurely after inclusion of 151 patients. The primary endpoint is the 2-year recurrence-free survival (RFS) rate. Secondary endpoints include overall survival, immunological response and safety.

Results: In January 2020, we performed a preplanned interim analysis. At that time, 102 patients reached mature data for primary endpoint analysis (recurrence of disease within 2 years of randomisation or at least 2-year follow-up). Thirty-eight percent of patients were female and the median age at start was 55.7 years (range 27-78). At inclusion, 51% of patients had stage IIIB disease and 49% stage IIIC disease. Two-year RFS rate was 21.4% in the treatment arm and 25% in the control arm (HR 1.05; 95% CI: 0.47-3.23), providing no statistically significant evidence of a treatment effect (p=0.67).

Conclusions: Our phase III clinical trial with adjuvant DC vaccination in stage IIIB and IIIC melanoma patients showed no benefit over placebo in terms of 2-year RFS. Correlative analysis of skin-test infiltrating lymphocytes for markers of immunological and clinical response are ongoing.

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1079MO Progression of BRAF mutant CNS metastases are associated with a transcriptional network bearing similarities with the innate PD-1 resistant signature (IPRES)

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Background: Melanoma CNS metastases are a common problem that causes high morbidity and mortality. Although first line dabrafenib-trametinib and ipilimumab-nivolumab (I-N) have similar intracranial response rates (50-55%), durable responses are only seen with combination immunotherapy and CNS resistance to BRAF-MEK inhibitors (BRAF-MEKi) usually occurs within 6 months. We sought to investigate the utility of I-N after BRAF-MEKi CNS progression and identify resistance mechanisms.

Methods: All patients receiving second/third line I-N for CNS metastases from 1/3/15 to 1/8/18 with prior progression on BRAF-MEKi and MRI brain staging were included. Modified intracranial RECIST was used to assess response. Formalin fixed paraffin embedded samples of BRAF V600 mutant CNS metastases naïve to treatment (n=18) or excised after progression on BRAF-MEKi (n=14) underwent whole transcriptome sequencing. Comparative analyses of CNS samples naïve to systemic treatment versus BRAF-MEKi progression was performed.

Results: Thirty patients received second/third line I-N with median CNS diameter of 21 mm. Modest efficacy of I-N after BRAF-MEKi progression was observed with an intracranial response rate of 4.8% (1/21) and median PFS of 5.5 weeks. Given the poor activity of I-N after BRAF-MEKi CNS progression we investigated the mechanisms that also conferred resistance to immunotherapy. We identified 179 differentially expressed genes (DEG) between naïve and BRAF-MEKi progression CNS metastases ($p < 0.05$, false discovery rate [FDR] < 0.1). Gene set enrichment analysis with KEGG, GO or Hallmark libraries did not identify distinct pathways. Enrichment of DEG from the Innate anti-PD1 Resistance Signature (IPRES) was identified ($p < 0.01$, FDR = 0.03). Macrophage associated chemokines and myeloid activation genes were upregulated in CNS progression samples. Histological assessment showed increased macrophage grading in BRAF-MEKi progression samples (mean 1.45 vs 0.45, p=0.009).

Conclusions: I-N after CNS BRAF-MEKi progression has modest intracranial activity. CNS metastases resistant to BRAF-MEKi showed expression of the IPRES gene signature and upregulation of myeloid cell activation markers.

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1080MO The value of local therapy in treatment of solitary melanoma progression upon immune checkpoint inhibition

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Background: Patients (pts) with stage IV melanoma can achieve long-term disease control through treatment with immune checkpoint inhibition (ICI). Disease progression in a single tumor lesion (solitary progression, SP) after initial response to ICI is often treated with local therapy. This study aimed to evaluate the benefits of local therapy for the treatment of SP during (on) or after cessation of (off) ICI.

Methods: Pts with stage IV melanoma with at least stable disease (SD) as best overall response (BOR) upon ICI and SP as first progressive event were retrospectively included from 17 centers in 9 countries.

Results: We included 294 pts with SP on anti-PD-1 (67%), anti-CTLA-4 (13%), anti-PD-1 + anti-CTLA-4 (15%) and other ICI combinations (5%). BOR prior to SP was SD (15%), partial response (55%) and complete response (30%). Local therapy was mainly surgery (56%), radiotherapy (35%) or both (5%). Median follow-up from start ICI was 43 months (m), median time to SP 13m and median time to second progression after treatment of SP (TTSP) 33m. Median overall survival (OS) was not reached, estimated 3-year OS was 79%. SP occurred in 143 pts on ICI (median 11m) and in 151 pts off ICI (median 17m from start ICI, 9m from stop ICI). SP was treated with local + systemic therapy (42%), local therapy (36%) or systemic therapy only (18%). Second progression was mostly progression at multiple sites (64% and 65% for SP on and off ICI). In pts with SP on ICI, median TTSP was 29m. Local therapy + ICI continuation (N=94) resulted in similar 3-year TTSP as local therapy (N=15) or ICI continuation only (N=14, P=0.971). OS at 3 years was superior for local therapy + ICI continuation (P=0.020). In pts with SP off ICI, median TTSP was 35m. ICI restart + local therapy (N=22, 85%) resulted in superior TTSP compared to local therapy (N=90, 41%) or ICI restart (N=18, 56%, P=0.002), without OS differences so far.

Conclusions: In pts with SP off ICI, the combination of local therapy + ICI restart was most successful in delaying further progression, but did not improve OS so far compared to single modality treatment. Local therapy + ICI continuation in pts with SP on ICI did not improve TTSP, but did improve OS. This indicates that local therapy can benefit pts.

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1081MO Efficacy of ipilimumab plus nivolumab or ipilimumab plus fotemustine vs fotemustine in patients with melanoma metastatic to the brain: Primary analysis of the phase III NIBIT-M2 trial

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Background: Brain metastases (BM) represent a high-unmet medical need, in which the therapeutic potential of immune-checkpoint(s) (ICI) is being actively investigated. Temozolomide and fotemustine (FTM) have been the therapeutic mainstay of melanoma (MM) patients (pts) with BM for over two decades. The Italian Network for Tumor Biotherapy (NIBIT)-M1 trial firstly demostrated signs of activity of ipilimumab (Ipi) combined with FTM in a subset of 20 MM pts with active BM (Di Giacomo, *Lancet Oncol*, 2012), with a 3-year survival rate of 28% (Di Giacomo, *Annals Oncol*, 2015). Two subsequent phase II studies reported the efficacy of Ipi combined with nivolumab (Nivo) in MM pts with asymptomatic BM (Twabi, *NEJM 2018*; Long, *Lancet Oncol* 2018). We here report the results of the primary analysis of the NIBIT-M2 study, the first phase III trial that explored the efficacy of Ipi *plus* Nivo in MM pts with BM.

Methods: The NIBIT-M2 is a phase III, multicenter, open-label study in MM pts with active, untreated, and asymptomatic BM. *BRAF* wilde type or mutant pts were randomized to receive FTM (ARM A), the combination of Ipi and FTM (ARM B), or the combination of Ipi and Nivo (ARM C). Primary objective was overall survival (OS); among secondary were intracranial (*i*) objective response rate (*i*ORR), *i* disease control rate (*i*DCR), and progression free survival (PFS).

Results: From January 2013 to September 2018, 96 MM pts were enrolled, 80 randomized, and 76 were treated: 23 in ARM A, 26 in ARM B, and 27 in ARM C. With a median follow-up of 39 months (mo), median OS was 8.5 mo (CI, 95%: 4.8-12.2) for ARM A, 8.2 mo (CI, 95%: 2.0-14.3) for ARM B, and 29.2 mo (CI, 95%: not yet evaluable) for ARM C. The *i*ORR was 0%, 19.2% and 44.4% in ARM A, B, and C, respectively. The *i*DCR was 26.1%, 34.6% and 55.6% in ARM A, B, and C, respectively. Median PFS was 3.0 mo (CI, 95%: 2.3-3.6), 3.3 mo (CI, 95%: 1.2-5.4), and 8.4 mo (CI,95%: 4.2-12.7), in ARM A, B, and C, respectively.

Conclusions: Unlike Ipi *plus* FTM, Ipi *plus* Nivo significantly (p=0.009) improves the long-term survival of MM pts with BM, compared to FTM. Ipi *plus* Nivo should represent the treatment of choice in first line MM pts with BM.

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1082MO 5-year characterization of complete responses in patients with advanced melanoma who received nivolumab plus ipilimumab (NIVO+IPI) or NIVO alone

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Background: 5-year outcomes of patients (pts) with a CR to NIVO+IPI or NIVO alone and factors associated with continued CR or relapse are unknown. The current pooled analysis addresses these key questions, including a 12-mo CR landmark analysis used to decrease the time guarantee bias.

Methods: In this post hoc analysis, 5-yr data were pooled from the phase III CheckMate 066 and 067 studies and the phase II CheckMate 069 study of pts with treatment-naive, advanced melanoma. Analyzed pts received either the approved regimen of NIVO+IPI followed by NIVO monotherapy or NIVO monotherapy. Characteristics and outcomes of pts with a CR (by RECIST) were investigated, including 12-mo landmark survival analyses to determine the likelihood of being alive at 5-y among pts in CR by 12 mo (to mitigate the time guarantee bias).

Results: Minimum follow-up was 60 mo since randomization of the last pt in each study; pooled median mo of follow-up was 63 for NIVO+IPI (n=409) and 64 for NIVO (n=526). CRs were demonstrated in 96 (23%) NIVO+IPI pts and 102 (19%) NIVO pts; of CR pts alive at 5 yrs, 75/79 (95%) and 85/91 (93%) had not received subsequent systemic therapy. Baseline characteristics significantly associated with CR (Table) were M stage (NIVO+IPI), PD-L1 $\geq$ 5% (NIVO), normal lactate dehydrogenase (LDH; both) and fewer disease sites (both). Median duration of CR and median time to subsequent systemic therapy were not reached in either group. Median mo (Q1, Q3) to CR was 9.1 (2.8, 23.1) for NIVO+IPI and 11.8 (5.8, 26.5) for NIVO alone. In pts in CR at 12-mo, 5-y OS for NIVO+IPI and NIVO respectively was 85% and 86%; PFS was 84% and 82%.

Table: 1082MO

	NIVO+IPI			NIVO		
	n/N	CR % (95% CI)	P-value	n/N	CR % (95% CI)	P-value
LDH status >ULN ≤ULN	16/138 80/269	12 (7-18) 30 (24-36)	<0.0001	19/191 81/317	10 (6-15) 26 (21-31)	<0.0001
LDH status > 2xULN ≤ 2xULN	2/43 94/364	5 (1-16) 26 (21-31)	0.0020	2/58 98/450	3 (<1-12) 22 (18-26)	0.0010
M stage M0 M1A M1B M1C	9/19 20/62 30/98 37/229	47 (24-71) 32 (21-45) 31 (22-41) 16 (12-22)	0.0004	8/35 15/70 30/110 49/311	23 (10-40) 21 (12-33) 27 (19-37) 16 (12-20)	0.0587
No. lesion sites 1 2-3 >3	53/128 36/211 7/70	41 (33-50) 17 (12-23) 10 (4-20)	<0.0001	40/130 50/303 12/91	31 (23-40) 16 (12-21) 13 (7-22)	0.0007
PD-L1 ≥5% <5%	20/92 64/266	22 (14-32) 24 (19-30)	0.6507	42/139 58/335	30 (23-39) 17 (13-22)	0.0017

ULN, upper limit of normal.

Conclusions: NIVO+IPI- or NIVO-treated pts in CR at 12 mo have a high likelihood of being alive at 5 y even without subsequent systemic therapy. Several baseline pt characteristics were associated with CR duration. Factors associated with CR may differ for NIVO+IPI and NIVO alone. Biomarker analyses are ongoing.

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1083MO Final results from ILLUMINATE-204, a phase I/II trial of intratumoral tilsotolimod in combination with ipilimumab in PD-1 inhibitor refractory advanced melanoma

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Background: Tilsotolimod (IMO-2125), an investigational Toll-like receptor 9 agonist, activates innate and adaptive immune responses and rapidly upregulates Type I IFN and dendritic cell activation following intratumoral injection. ILLUMINATE-204 was a phase 1/2 study of tilsotolimod with ipilimumab in patients with advanced melanoma following progression on or after anti-PD-1 therapy.

Methods: Adults with unresectable or metastatic melanoma that progressed on or after a PD-1 inhibitor, an accessible tumor for intratumoral administration of tilsotolimod, and $\leq$ 2 lines of prior therapy ($\leq$ 3 if BRAF-mutant) were eligible. Prior ipilimumab was allowed. Tilsotolimod was administered to a single tumor during weeks 1, 2, 3, 5, 8, and 11; ipilimumab was administered per the product label. The primary objective of the phase II portion was to assess preliminary clinical activity at the recommended phase II dose (RP2D).

Results: A total of 62 patients were treated with tilsotolimod in combination with ipilimumab. Of these, 52 received the RP2D of 8 mg, and 49 were evaluable for efficacy. The median OS was 21.0 months (95% confidence interval (CI): 9.8 - not reached [NR]), and the overall response rate per RECIST v1.1 was 22.4% (95% CI: 11.8 - 36.6), including 2 complete responses. Median duration of response was 11.4 months (95% CI: 3.3 - NR) with 7/11 responses lasting $\geq$ 6 months. The disease control rate was 71.4% (95% CI: 56.7 - 83.4). Tumor reduction was observed in injected and non-injected lesions. Analysis of biopsies showed rapid local IFNα gene expression, dendritic cell maturation, and expansion of shared CD8+ T cell clones in injected and non-injected tumors. Grade $\geq$ 3 AEs were observed in 48% (30/62) of patients, most commonly increased ALT and AST and colitis, and 26% experienced immune-related AEs. No AEs led to treatment discontinuation or death.

Conclusions: Tilsotolimod with ipilimumab was generally well-tolerated and demonstrated efficacy in anti-PD-1-refractory advanced melanoma. Activity was observed in injected and non-injected lesions. A phase III study of this combination compared with ipilimumab alone (ILLUMINATE-301; NCT03445533) is ongoing.

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Legal entity responsible for the study: Idera Pharmaceuticals.

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Disclosure: C. Haymaker, C. Bernatchez: Advisory/Consultancy: Idera Pharmaceuticals. R.H.I. Andtbacka: Advisory/Consultancy: Aduro; Advisory/Consultancy: Merck and Co; Advisory/Consultancy: Novartis; Advisory/Consultancy: OncoSec; Advisory/Consultancy: Pfizer; Advisory/Consultancy: Takara. D.B. Johnson: Advisory/Consultancy, Research grant/Funding (self): Bristol-Myers Squibb; Research grant/Funding (self): Incyte; Advisory/Consultancy: Array Biopharma; Advisory/Consultancy: Merck and Co; Advisory/Consultancy: Novartis; Advisory/Consultancy: Janssen. S. Rahimian, S. Chunduru: Shareholder/Stockholder/Stock options, Full/Part-time employment: Idera Pharmaceuticals. I. Puzanov: Advisory/Consultancy: Amgen. J. Markowitz: Research grant/Funding (institution): Morphogenesis; Research grant/Funding (institution): Jackson Labs; Advisory/Consultancy: Newlink Genetics; Advisory/Consultancy: Array Biopharma. A. Diab: Advisory/Consultancy, Research grant/Funding (self): Idera Pharmaceuticals; Advisory/Consultancy, Research grant/Funding (self): Nektar Therapeutics; Advisory/Consultancy, Research grant/Funding (self): Bristol-Myers Squibb; Advisory/Consultancy: Jounce Therapeutics; Advisory/Consultancy: Novartis; Advisory/Consultancy: Array BioPharma. All other authors have declared no conflicts of interest.

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1084P Cosibelimab, an anti-PD-L1 antibody, in metastatic cutaneous squamous cell carcinoma (mCSCC): Preliminary safety and efficacy results from a phase I clinical trial

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Background: Cosibelimab is a high affinity, fully-human IgG1 monoclonal antibody that directly binds to programmed death ligand-1 (PD-L1) and blocks its interaction with the programmed death receptor-1 (PD-1) and B7.1 receptors to restore an anti-tumor immune response. Cosibelimab has the additional benefit of a functional Fc domain capable of inducing antibody-dependent cellular cytotoxicity against tumor cells. Study CK-301-101 is a global, multicenter, multicohort trial that is enrolling patients (pts) with select advanced cancers, including a pivotal cohort of mCSCC (nodal and/or distant). Here we present preliminary safety data from the trial and efficacy data from the mCSCC cohort.

Methods: Eligible mCSCC pts (aged $\geq$18 years with histologically confirmed mCSCC and Eastern Cooperative Oncology Group performance status of 0-1) received a fixed dose of 800 mg cosibelimab administered intravenously every two weeks. The primary efficacy endpoint of objective response rate (ORR; complete response + partial response) by independent central review as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 is intended to provide the primary evidence of efficacy for product registration. The safety analysis includes all pts treated with at least one dose of cosibelimab.

Results: As of 17 April 2020, 103 pts have been treated, of which 92% experienced $\geq$1 treatment-emergent adverse event (AE), 36% experienced a grade $\geq$3 AE, and 6% experienced a grade $\geq$3 drug-related AE. The most common treatment-emergent AEs were fatigue (24%), anemia (22%), nausea and rash (17% each) and the most common drug-related AEs were rash (15%) and fatigue (13%). In 32 mCSCC pts evaluable for response, ORR based on investigator assessment of tumor response was 47%, including 3 complete responses and 12 partial responses. At the time of analysis, median duration of response was not reached, with 14/15 (93%) responses ongoing and 9 responses $\geq$6 months (longest, 14+).

Conclusions: Cosibelimab has a predictable and manageable safety profile and demonstrated robust clinical activity in mCSCC pts, including durable complete and partial responses. Enrollment is ongoing and updated results will be presented.

Clinical trial identification: NCT03212404.

Legal entity responsible for the study: Checkpoint Therapeutics, Inc.

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Disclosure: P. Clingan: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Research grant/Funding (institution): Merck; Research grant/Funding (institution): AbbVie; Research grant/Funding (institution): Eli Lilly; Research grant/Funding (institution): Bristol-Myers Squibb. D. Brungs, A.M. Mant, A. Tazbirkova, P. Koralewski: Research grant/Funding (institution): Checkpoint Therapeutics, Inc. R. Ladwa: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Honoraria (self), Advisory/Consultancy: Roche; Honoraria (self), Advisory/Consultancy: Merck; Honoraria (self), Advisory/Consultancy, Travel/Accommodation/Expenses: Ipsen; Advisory/Consultancy: Sanofi. M. McGrath: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Advisory/Consultancy: Bristol Myers. I. Lugowska: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Honoraria (self), Research grant/Funding (institution): Bristol-Myers Squibb; Honoraria (self): Merck; Honoraria (self), Research grant/Funding (institution): Roche; Honoraria (self): Amgen; Honoraria (self): Janssen; Honoraria (self), Research grant/Funding (institution): Novartis. C. Charoentum: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Research grant/Funding (institution): Roche; Research grant/Funding (institution): AstraZeneca. A. Dechaphunkul: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Travel/Accommodation/Expenses: Eisai. V. Sriuranpong: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Honoraria (self), Research grant/Funding (institution): AstraZeneca; Honoraria (self), Research grant/Funding (institution): Novartis; Honoraria (self), Research grant/Funding (institution): Roche; Honoraria (self), Research grant/Funding (institution): Pfizer; Honoraria (self): Sanofi; Honoraria (self), Research grant/Funding (institution): Eisai; Honoraria (self), Research grant/Funding (institution): Boehringer; Honoraria (self), Research grant/Funding (institution): Taiho; Honoraria (self), Research grant/Funding (institution): Merck; Honoraria (self): Bristol Myers; Advisory/Consultancy: Amgen. J. Oliviero: Shareholder/Stockholder/Stock options, Full/Part-time employment, Officer/Board of Directors: Checkpoint Therapeutics, Inc. D.L. Harris: Research grant/Funding (institution): Checkpoint Therapeutics, Inc.; Research grant/Funding (institution): Merck; Research grant/Funding (institution): Roche; Research grant/Funding (institution): Targovax.

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1085P Health-related quality of life in stage III melanoma patients treated with neoadjuvant ipilimumab and nivolumab followed by index lymph node excision only versus therapeutic lymph node dissection: 24-week results of the PRADO trial

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Background: Neoadjuvant ipilimumab + nivolumab induces high pathologic response rates with high relapse free survival (RFS). Response appears concordant among nodes in the tumor bed, such that a therapeutic lymph node dissection (TLND) may not be required for patients (pts) achieving a major pathologic response (MPR, $\leq$10% viable tumor cells) in a single sampled node. In the PRADO trial, TLND was omitted in pts achieving an MPR after resection of just their index lymph node (ILN, the largest LN marked prior to neoadjuvant therapy). We provide 24-week Health Related Quality of Life (HRQoL) results of pts undergoing ILN procedure only versus pts without MPR who underwent TLND.

Methods: HRQoL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire-C30 and melanoma surgery specific questions of the Functional Assessment of Cancer Therapy-Melanoma. A generalized estimation equation was used to assess the difference in HRQoL outcomes between pts who underwent TLND versus those who did not. Differences were adjusted for age, gender and follow-up (FU). Pathologic response and additional adjuvant treatment were not included at this stage.

Results: For the 99 pts enrolled in PRADO, questionnaire (QLQ) completion rates were: 91% at baseline and 93%, 90%, 67% at week 6, 12 and 24, respectively. Patients were included if they filled in at least 2 QLQ's. Median age was 59 (range, 19 – 86) years. Over the FU period of 24 weeks, pts who went on to TLND (n=30) scored significantly lower on global (difference (diff= -6.82; p=.025), physical (diff= -8.74; p<.001), and role functioning (diff=-10.74; p=.012), but higher in symptom burden of insomnia (diff= 17.61; p<.001), pain (diff= 8.60; p=.002), fatigue (diff= 8.98; p=.024), constipation (diff= 8.43; p=.001) and melanoma surgery related symptoms (-2.55; p=.001) than pts who did not (n=61).

Conclusions: Stage 3 melanoma patients with MPR following neoadjuvant immunotherapy who have reduced extent of surgery have significantly better HRQoL scores. By September 2020, the majority of PRADO pts will have reached 36 weeks FU. This data will also be presented.

Clinical trial identification: Clinical trial information OpACIN-neo/PRADO extension cohort NCT02977052.

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1086P Cemiplimab for advanced cutaneous squamous cell carcinoma: Real life experience

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Background: Patients (pts) with advanced cutaneous squamous cell carcinoma (CSCC) have a poor prognosis. A French early access program (EAP) allowed access to cemiplimab (CEM), a PD-1-blocking antibody, (3 mg/kg/2 wks) in 247 pts with locally advanced (la) or metastatic (m) CSCC.

Methods: This was a retrospective analysis of pts with la/m CSCCs treated with CEM from 45 centers. The primary endpoint was best response rate (RR); secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR) and safety. Response was assessed by investigators. Adverse events (AEs) were graded according to the CTCAEv5. PFS, OS and DOR were estimated using Kaplan—Meier analysis. Data cutoff was 05/05/20.

Results: Of 247 pts enrolled between 8/18 and 10/19, files of 193 pts (141M/52F; mean age 77 yrs ±13) were collected. Half pts received CEM as a 1st line of systemic treatment. 68% of primary CSCCs were located on head and neck. 37% of pts had la CSCC; 36% had regional disease and 27% distant metastases. 26% of pts were immunocompromised. 72% of pts had PS 0/1. Median number of CEM infusions was 10 (0-35). Among 188 pts who received >1 infusion, the best RR was 50% (CI95% 43-57%, 40 CR, 54 PR); DCR was 60%. Median follow-up was 12 mo (1-20). Median PFS was 11 mo (8—NE), median OS and DOR were not reached; 65% (CI95%, 57-73%) of pts were alive 1 yr after starting CEM. Treatment-related Aes (TRAE) were reported in 49 (26%) pts, the most frequent (>2%) being fatigue, hypothyroidism and cholestasis. A total of 18 (9%) pts experienced ≥1 gr. 3—4 TRAE. There were no treatment-related deaths reported, and 10 (5%) pts discontinued therapy because of TRAE (cholestasis and/or cytolysis (3 cases), anorexia, fatigue, anemia, kidney failure, polyarthritis, DRESS syndrome, colitis).

Conclusions: These results strongly suggest that cemiplimab, in the first French pts treated in real life setting, provided a similar benefit to that observed in clinical trials.

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1087P Time to clinically meaningful changes in pain in patients with advanced cutaneous squamous cell carcinoma treated with cemiplimab in a phase II clinical trial

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Background: Cemiplimab, a PD-1 inhibitor, is indicated for treatment of cutaneous squamous cell carcinoma (CSCC) in patients (pts) with metastatic (mCSCC) or locally advanced (laCSCC) disease not eligible for curative surgery/radiation. Cemiplimab resulted in RECIST objective response rate (tumour response; complete+partial) of 44.0%, with median times to tumour response of 2.0 months and progression-free survival (PFS) of 18.4 months; the safety profile was consistent with other anti—PD-1 inhibitors. Cemiplimab-treated pts achieved clinically meaningful (CM) reductions in pain measured using the patient-reported EORTC QLQ-C30 pain domain. Interpretation of change in pain was further characterised by the relationship between time to a CM change in pain and tumour response.

Methods: Adults (N=193) with confirmed diagnosis of invasive CSCC received IV cemiplimab 3 mg/kg Q2W (mCSCC n=59; laCSCC n=78) or 350 mg Q3W (mCSCC n=56). The QLQ-C30 was administered at baseline (BL) and day 1 of each treatment cycle. Kaplan—Meier (KM) survival analysis (with censoring at drop-out) was used to estimate time to 1st CM (≥10-point) reduction (improvement) or increase (worsening) in QLQ-C30 pain scores. Pain medication use was captured over the treatment period.

Results: Compared to non-responders, pts with tumour response reported a CM reduction in pain from BL at 1st tumour response (cycle 2) ($P<0.0001$) (Table); pain reduction was maintained at least through cycle 5 and was independent of opioid pain medication use. KM analysis showed median time to 1st CM pain improvement and 1st CM pain worsening (Table) approximated median times to tumour response and PFS, respectively.

Conclusions: In cemiplimab-treated CSCC pts, early pain reduction tracked with 1st tumour response, and pain worsening with PFS. These results suggest that changes in pain may correlate with tumour response.

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1088P Efficacy of post-operative radiation therapy in non-metastatic Merkel cell carcinoma: A registry-based analysis

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Background: Merkel cell carcinoma (MCC) is a rare aggressive neuroendocrine tumor of the skin. The optimal management of non-metastatic MCC is still unclear but it is crucial to decrease relapse risk and improve survival. We sought to assess the efficacy of radiation therapy (RT) of MCC without distant metastases (M0 MCC) by analyzing data from the Surveillance, Epidemiology, and End Results (SEER) registry.

Methods: We extracted from the SEER Registry data about M0 MCC patients, identified by the 8247 ICD-03 code, irrespective of the site of origin. We collected data about stage at diagnosis, site and size of primary, extent of surgery, lymph node directed surgery, number of involved lymph nodes, RT, and survival outcome. Primary endpoint was overall survival (OS).

Results: Of 9773 MCC patients in the SEER registry, 2335 were M0 MCC (63% male, median age 77 years). MCC originated from skin of the limbs in 994 (61.6%), head and neck district in 386 (23.9%), and trunk in 234 (14.5%). Lymph nodes were negative in 1577 patients (67.5%), while among the 687 (32.5%) MCC with nodal involvement this was microscopic in 214, macroscopic in 233, not otherwise specified (NOS) in 240; 71 had in-transit metastases. Post-operative RT was performed in 1212 (51.9%) patients. Overall, median OS of M0 MCC patients was 56 months (95%CI: 50.7-61.3) and was affected by age, site, tumor size, nodal involvement, type of surgery of primary and RT (HR for RT: 0.65 [95%: 0.53-0.79]; $p<0.001$) at multivariate analysis. In the 1577 with

Table: 1087P

	Clinical responders (complete+partial)	Clinical non-responders (stable+progressive)	All
Baseline pain score, mean ± SD (n)	26.1 ± 28.4 (81)	33.7 ± 31.6 (87)	29.8 ± 30.4 (152)
Change from baseline in pain score at 1st tumour response, n	81	71	–
Least squares mean change ± SE	−13.8 ± 1.7	−3.3 ± 2.1	–
Least squares mean (95% CI) difference vs non-responders	−10.5 (−15.6, −5.3)	–	–
Median time to tumour response, months (n)	2.0 (85)	–	–
Median progression-free survival, months (n)	–	–	18.4 (193)
Median time to 1st clinically meaningful pain improvement, months (n)	2.1 (51)	–	2.1 (100)
Median time to 1st clinically meaningful pain worsening, months (n)	14.8 (77)	–	12.9 (142)

negative lymph nodes, after correcting for confounding factors, OS was affected by age, sex, site, size of primary, extent of surgery and RT (HR for RT: 0.63 [95%: 0.47-0.82]; p<0.001). Among 687 patients with positive lymph nodes (67% male, median age 74), at multivariate analysis OS was affected by age, nodal involvement, number of positive lymph nodes and RT (HR for RT: 0.67 [95%CI: 0.49-0.92]; p=0.012).

Conclusions: RT was associated with a decreased risk for death in M0 MCC, irrespective of nodal status.

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1089P POD1UM-201: A phase II study of retifanlimab (INCMGA00012) in advanced or metastatic Merkel cell carcinoma (MCC)

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Background: Retifanlimab is a humanized IgG4 monoclonal antibody targeting human programmed cell death protein (PD)-1. Retifanlimab monotherapy as 500 mg intravenously (IV) every 4 weeks (Q4W) is under investigation in phase II studies in solid tumors. Here we report preliminary clinical activity and safety results from POD1UM-201, a phase II, open-label, single-arm, multicenter study assessing efficacy and safety of retifanlimab in advanced/metastatic MCC.

Methods: Eligible patients (pts) have unresectable locally advanced/metastatic MCC, ECOG PS ≤1, measurable disease per RECIST v1.1, are either chemotherapy (chemo)-naïve or have received ≤3 prior chemo regimens, and have had no prior treatment with anti−PD-1/anti−PD-L1 therapy. The primary endpoint is overall response rate (ORR) per RECIST v1.1 in chemo-naïve pts. Secondary endpoints include safety in all pts, and duration of response (DOR), disease control rate, progression-free survival, and overall survival in chemo-naïve pts.

Results: As of January 8, 2020, 27 pts with MCC had received retifanlimab 500 mg IV Q4W (22 chemo-naïve, 5 refractory, all stage IV). Of the 22 chemo-naïve pts enrolled, 18 have had ≥1 on-study tumor assessment or discontinued. There are 10 (56%) responders (investigator assessed) with 2 (11%) complete responses and 8 (44%) partial responses. Of these, 6 are confirmed and 4 are unconfirmed ongoing responses. Three pts (17%) have stable disease. Among all treated pts (n=27), 16 (59%) had a treatment-emergent adverse event (TEAE); 6 (22%) were ≥Grade 3, 11 (41%) had a treatment-related TEAE (TRAE), 3 (11%) of which were ≥Grade 3. The most common TRAEs were asthenia and pruritus (n=3 each). Seven (26%) had a TEAE of special interest (the only immune-related AE occurring in >1 pt was hypothyroidism [n=2]). Two pts (7%) discontinued treatment due to TEAEs (radiculopathy and polyarthritis). No fatal TEAEs have been reported.

Conclusions: Initial results demonstrate promising activity and safety of retifanlimab in pts with advanced or metastatic chemo-naïve MCC. Updated results from a pre-planned analysis for futility will be presented at the meeting.

Clinical trial identification: NCT03599713, July 26, 2018; EudraCT 2018-001627-39, 2018-12-10.

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1090P Real-world (RW) clinical outcomes in patients (pts) with locally advanced (LA) or metastatic Merkel cell carcinoma (mMCC) treated in United States (US) oncology clinical practices: Results from SPEAR-Merkel

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Background: MCC is a rare, aggressive skin cancer with high disease-associated mortality. The approval of immuno-oncology (IO) therapies has altered the standard of care and improved outcomes in pts with LA and mMCC. SPEAR-Merkel (Study informing treatment Pathway dEcisions in Merkel cell cARcinoma) assessed RW clinical outcomes in pts with LA and mMCC initiating first-line (1L) treatment with avelumab (A-IO), non-avelumab IO (NA-IO), or chemotherapy (C) in the community setting in the US.

Methods: Adult pts with LA or mMCC who began 1L treatment with A-IO, NA-IO, or C from 1 Jan 2017 to 31 Mar 2019 were identified from the US Oncology Network electronic healthcare record database and followed through 30 Sep 2019. Baseline characteristics and RW overall response rate (ORR) were analyzed descriptively. Kaplan-Meier methods were used to evaluate progression-free survival (PFS), overall survival (OS), and duration of therapy (DOT).

Results: The study included 94 pts (median age, 73 years; 68% male); 28 A-IO, 26 NA-IO, and 40 C. Median follow-up (months) was 11.2, 9.8, and 10.7 in A-IO, NA-IO, and C pts, respectively. The majority of pts were immunocompetent (>85%), and 29% had LA MCC prior to 1L treatment (A-IO, 32.%; NA-IO, 31%; C, 25%). Clinical outcomes are reported in the table.

Table: 1090P

	A-IO N=28	NA-IO N=26	C N=40
ORR (physician assessed)[a]	64.3 (44.1-81.4)	61.5 (40.6-79.8)	42.5 (27.0-59.1)
Median PFS[b]	11.4 (5.3-NR)	8.1 (3.0-NR)	6.1 (3.6-10.6)
PFS rate[c]	67.9 (47.3-81.8)	57.7 (36.8-73.9)	50.0 (33.8-64.2)
Median OS[b]	20.2 (11.1-NR)	NR (5.5-NR)	14.7 (8.8-NR)
OS rate[c]	85.7 (66.3-94.4)	69.2 (47.8-83.3)	77.5 (61.2-87.6)
Median DOT[b]	10.5 (5.3-14.3)	7.3 (2.5-18.2)	2.2 (1.9-3.5)

NR, not reached [a] (95% CI), % [b] (95% CI), months [c] (95% CI) at 6 months, %

Conclusions: This is the first RW study to examine outcomes in pts with LA or mMCC treated with A-IO or NA-IO. Although the sample size is small, this study suggests consistent outcomes in A-IO and NA-IO pts, slightly favoring A-IO. Response rates with IO were higher than with C, as determined by pivotal trials. These RW data suggest there may be an opportunity to improve outcomes for pts treated with C.

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1091P Performance of Salamanca's refinement of the AJCC8 for T3 cutaneous squamous cell carcinoma (CSCC), versus the Brigham and Women's Hospital's alternative staging system and the Tübingen's alternative staging system for high-risk CSCC

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Background: The AJCC8 shows heterogeneity for high-risk cutaneous squamous cell carcinoma (CSCC). The Brigham and Women's Hospital (BWH) and the Tübingen's stratification systems offer different proposals to AJCC8 and our group identified prognostic subgroups within T3-AJCC8, where most high-risk CSCCs are classified. The objective of this study was to compare the distinctiveness, homogeneity, monotonicity, prognostic accuracy and concordance of these alternative staging systems for the subset of high-risk CSCC staged as T3-AJCC8.

Methods: Retrospective cohort study of 196 cases of high-risk CSCC. All tumors were classified according the three alterative staging systems. Pair-wise comparison was performed through McNeemar test, and distinctiveness, homogeneity and monotonicity of the staging systems were also assesed. The prognostic accuracy was compared by means for Akaike AIC and BIC indexes and the concordance among staging systems was later compared by means of Harrell's C-index and Gonen and Heller's concordance probability estimation (CPE).

Results: The AJCC8-T3b/T3c represented 51.5% of the total cases, the BWH-T2b/T3 47.4% and the Tübingen system (3-4 points) 34.2%. BWH's and Salamanca's showed some overlap between each other and differ from Tübingen's. The prognostic accuracy revealed that Tübingen's is more efficient for local recurrence, and Salamanca's and BWH's are better for major events and for disease-specific death. Concordance analysis is better with any of the alternative systems than with the official AJCC8.

Conclusions: Alternative staging systems may partially overcome the heterogeneity and low prognostic accuracy of AJCC8 and stratify high risk CSCC more precisely. The combination of risk factors should be considered in future staging systems for CSCC.

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1092P Non-progression with avelumab treatment in patients with metastatic Merkel cell carcinoma (mMCC) is associated with a clinically meaningful better health-related quality of life compared with progressive disease

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Background: Longitudinal assessment of health-related quality of life (HRQoL) is important to increase our understanding of the trajectory of patients' self-reported health status associated with cancer treatment. In this international, single-arm, open-label, phase II trial (JAVELIN Merkel 200; NCT02155647), treatment-naïve patients with mMCC received first-line treatment with avelumab 10 mg/kg every 2 weeks. The study aimed to evaluate patients' HRQoL over a 15-month follow-up period.

Methods: HRQoL was assessed using disease-specific (FACT-M) and generic (EQ-5D visual analogue scale [EQ VAS]) questionnaires at baseline, week 7, and every 6 weeks thereafter until progressive disease (PD) and/or treatment discontinuation. Mixed-effect models for repeated measures (MMRM) analyses were conducted using all HRQoL data provided to evaluate changes over time. The impact of PD on HRQoL was also assessed through these models by dichotomizing the sample into PD and non-PD (stable disease or partial/complete response) groups.

Results: In 116 enrolled patients, 538 HRQoL assessments were analyzed; HRQoL questionnaire compliance rate was >75% overall. HRQoL was relatively stable across all patients, with 9 of 12 FACT-M subscales and EQ-VAS showing a smaller change from baseline than the minimal important difference (MID) threshold, indicating no clinically relevant change. When comparing PD vs non-PD groups, clinically meaningful differences reaching MID threshold were observed across almost all (10/12) FACT-M subscales and EQ VAS. For example, for the FACT-M total score (MID=5), the difference was estimated at 9.52 (95% CI: 6.05, 12.98), favoring the non-PD group.

Conclusions: These findings show unique longitudinal HRQoL data for treatment-naïve patients with mMCC treated with avelumab. Despite a decreasing sample size over the 15-month study period, as expected in the context of an aggressive cancer such as mMCC, HRQoL scores were relatively stable over time. Non-PD with avelumab treatment was associated with statistically and clinically meaningful better HRQoL compared with PD.

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Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

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1093P The features of the tumour microenvironment and the tumour budding identify prognostic subgroups in high-risk cutaneous squamous cell carcinoma

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Background: In recent years, tumor microenvironment (TMe) and tumor budding (TB) have gained greater attention in the prognostication of tumors, including cutaneous squamous cell carcinoma (CSCC). A better characterization of TMe and TB might increase our knowledge on high-risk CSCC and improve future staging systems. Objective**:** To define prognostic subgroups according to the features of the TMe and the TB.

Methods: The features of TMe (peritumoral inflammatory infiltrate, tumoral stroma and desmoplasia) and TB were evaluated in a retrospective cohort study of 190 primary HR-CSCC. Unsupervised multidimensional scaling (MDS) analysis was conducted to identify subgroups based on the combination of these risk factors. The time-dependent outcomes of the groups were analyzed considering competing risks. Multivariate analysis was conducted to check for the independence of TMe and TB in prognosis together with the AJCC8 risk factors.

Results: The features that define TMe and TB were associated among them and thus we aimed to search for clusters based on the aforementioned variables. MDS analysis identified three subsets of CSCC according to TMe and TB. Group-3 (very high risk) showed absent peritumoral inflammation, aberrant stroma, desmoplasia and tumor budding at the same time; Group-2 (high risk) displayed any but not all of these risk factors combined; and Group-1 (low risk) was characterized by the absence of all these risk factors. The combination of the TMe+TB subgroups with the AJCC8 high-risk features in multivariate Cox regression models, demonstrated the independence of TMe and TB in the prognosis of CSCC. Indeed, the very-high risk group showed 2.5 times greater risk for local recurrence and 6.5 times greater risk for metastasis and disease-specific death compared with the low risk group in the multivariate analysis.

Conclusions: There is statistically significant evidence to conclude that the features of TMe and the TB may identify prognostic subgroups in HR-CSCC, and they may be considered for upcoming staging systems.

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1094P Demographics, prior therapies and reasons for cemiplimab treatment: Prospective cemiplimAb-rwlc survivorship and epidemiology (C.A.S.E.) study in patients with advanced cutaneous squamous cell carcinoma (CSCC)

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Background: Limited data exist on the clinical characteristics, management, disease progression and survivorship of patients with advanced CSCC in real-world clinical practice. We describe baseline demographics for the first set of patients enrolled in the C.A.S.E. study.

Methods: C.A.S.E. is a prospective, multicentre, longitudinal study evaluating the efficacy, safety, disease evolution, survivorship and quality of life in patients with advanced CSCC who initiate treatment with cemiplimab. Key endpoints include effectiveness of cemiplimab treatment, safety, patient reported outcomes, treatment adherence and health resource utilisation.

Results: As of 31 Jan, 2020, 61 patients were enrolled (median age: 78 years [IQR: 70—86]; 74% male; 97% Caucasian; and 21% immunocompromised or immunosuppressed including 5% who had solid organ transplant). 56% of patients had locally advanced CSCC and 44% had metastatic CSCC. 69% of patients had a head and neck primary CSCC tumour location. 54% of patients had multidisciplinary input in their advanced CSCC management. 75% had prior CSCC-related surgery and 41% received CSCC-related radiotherapy (RT). CSCC tumours were classified histologically as well differentiated, moderately differentiated, poorly differentiated and unknown for 23%, 38%, 20% and 20% of tumours. 21% of tumours had perineural invasion and 8% had histological heterogeneity. The most common reasons for cemiplimab treatment were locally advanced CSCC that is not a candidate for curative surgery or curative RT (34%), not a candidate for curative surgery (30%), local-regional disease (23%), metastatic disease (23%) and patient preference (15%).

Conclusions: This initial demographic analysis of patients with advanced CSCC receiving cemiplimab in real-world practice indicates that most patients were male, elderly, with 21% being immunosuppressed or immunocompromised to varying degrees. Only 54% of cases had multi-disciplinary input in their disease management. These data also suggest there are varying factors affecting treatment decisions in real-world clinical setting.

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1095P Exosomal microRNA in serum is a prognostic factor in cutaneous squamous cell carcinoma

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Background: Functional microRNA(miRNAs) is located in the area of the gene related to cancer, such as inside of oncogenes and tumor suppressor genes, loss of heterozygocity or fragile site. There are many studies show that abnormal increase expression of miRNAs when cancer occurs. While some miRNAs commonly suppress abnormal expression of tumors, they can also infer the orgin of tumor tissues because they are more often representative of unique miRNA depending on type of tumor. In many case, the miRNAs expression patterns provide more characteristic information about tumors than messenger RNA expression profinling. The miRNAs expression patterns, which have changed with tumor types, provide clue that can serve as a biological markers for diagnosis, determining the outcome of disease, and predicting treatment responses. Indeed, several studies have reported thatextracellular miRNA is related to the prognosis of disease in some cancers, such as colon cancer and breast cancer. However, so far, there is no study that has been no defenitive study on how exosomal miRNAsare related to progrosis in cutaneous squamous cell carcinoma. We studied the association between the patient's prognosis and miRNAs detected in cancer tissue and blood serum.

Methods: We analyzed 35 patients who have various stage of cutaneous squamous cell carcinoma. Cancer tissue and serum samples were sequentially obtained. The miRNAs were prified from serum exosome and cancer tissues, and miRNAs sequencing was performed. The miRNAs expression profiles and copy number variations were observed using next generation sequencing (Hiseq, illumina inc) in 35 cancer tissues and serum samples. We validated miRNAs change and patient's prognosis.

Results: miR-142-5p cluster expression level in serum exosome and cancer tissue was most correlated with poor prognosis of cutaneous squamous cell carcinoma. Exosomal miR-142-5p expression level in serum were significantly higher($P < 0.01$) in patients with late stage than in patients with early stage. Also, the patients with recurrence showed high level of miR-142-5p.

Conclusions: miR-142-5p expression level may be an important marker for predicting the patient's prognosis and deciding whether undergo additional systemic chemotherapy after surgery.

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1096P Clinicopathologic risk factors for large cell transformation in patients with Sezary syndrome

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Background: Large cell transformation (LCT) of Sezary Syndrome (SS) is associated with an aggressive clinical course. To date, there are no rigorous studies identifying risk factors for the development of this phenomenon. We aim to characterize the clinicopathologic risk factors that may predispose patients with SS to develop LCT.

Methods: We retrospectively evaluated all SS patient records available in the Michigan Medicine Cancer Registry from 2010-2019. The Mann-Whitney U test and Fisher exact test were used to compare age, sex, race, time to diagnosis, stage, total body surface area (TBSA) involvement, pathologic features, complete blood counts, flow cytometry data, and T cell receptor rearrangements. The Kaplan-Meier method and log-rank test were used to assess overall survival (OS). Univariate analyses were conducted for endpoints of LCT and OS and visualized with Forest plots using the "survival" and "forestplot" packages in R.

Results: Of the 28 SS patients included in the analysis, eight patients with LCT were identified, and 20 with no large cell transformation (NLCT). Mean age at SS diagnosis was 74 for LCT and 63 for NLCT. Mean peak LDH before LCT ($p = 0.0012$), mean maximum TBSA involvement before diagnosis of LCT ($p = 0.0114$), absolute $CD8^+$ cell count on flow cytometry or on biopsy at diagnosis of SS ($p = 0.0455$), presence of Langerhans cell hyperplasia ($p = 0.0171$), and presence of ulceration on biopsy ($p = 0.0034$) were clinicopathologic variables identified as differing significantly between the two groups. On univariate analysis, increased TBSA involvement (HR 1.043 per unit increase, 95% CI 1.001 − 1.081, $p = 0.018$) and increased peak LDH prior to LCT diagnosis (HR 1.002 per unit increase, 95% CI 1.001 − 1.003, $p = 0.002$) were identified as poorly prognostic, while unit increase in $CD8^+$ absolute cell count at diagnosis of SS (HR 0.988, 95% CI 0.976 − 0.999, $p = 0.041$) was identified as protective for development of LCT. There was no survival difference identified between patients with "High" vs. "Low" $CD8^+$ cell counts, or between LCT and NLCT groups.

Conclusions: Maximum TBSA involvement, peak LDH, presence of ulceration, Langerhans cell hyperplasia, and decreased levels of $CD8^+$ cells in the peripheral blood may predict the development of LCT in patients with SS.

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1097P 4-year relapse-free survival (RFS), overall survival (OS) and long-term toxicity of (neo)adjuvant ipilimumab (IPI) + nivolumab (NIVO) in macroscopic stage III melanoma: OpACIN trial

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Background: Neoadjuvant (neoadj) IPI + NIVO showed in different trials in almost 200 patients (pts) a pathologic response rate of 71-78%. The investigator-initiated OpACIN trial was the first trial testing neoadj IPI + NIVO and therefore has the longest follow-up (FU). Pathologic responses were observed in 7/9 pts (78%) in the neoadj arm, 1 pt was non-evaluable. The question remains how durable these responses are. Here we present the 4-year safety and survival data from this trial.

Methods: Twenty macroscopic stage IIIB-C melanoma pts were included in the phase 1b feasibility OpACIN trial between Augustus 2015 and October 2016. Pts were randomized to receive either IPI 3 mg/kg + NIVO 1 mg/kg 4 cycles adjuvant (adj) after lymph node dissection or split 2 cycles neoadj and 2 adj. The 4-year RFS and OS rates were estimated using the Kaplan Meier method. All comparative efficacy endpoints are descriptive since the trial was not powered for comparison of the arms.

Results: None of the 7 pts with a pathologic response in the neoadj arm have relapsed after a median FU of 48.0 months (minimum 38.1 months FU of pts alive). Within the neoadj arm only the two non-responding pts and the one non-evaluable pt have relapsed, 4 pts have relapsed in the adj arm. Estimated 4-year RFS rate was 60% for the neoadj arm and 60% for the adj arm, the 4-year OS rates were 90% and 70%, respectively. All grade 3-4 immune-related adverse events, initially for both arms reported in 90% of pts, have recovered to grade 1 or less, except for the grade 2 endocrinopathies requiring hormonal replacement therapy that are ongoing within 8 (50%) of the 16 pts alive.

Conclusions: The 4-year survival data of OpACIN indicate that pathologic response upon neoadj IPI + NIVO in macroscopic stage III melanoma is an excellent surrogate marker for long-term outcome (RFS and OS), as none of the responders has relapsed. In combination with data from other neoadj trials, these data suggest that pathologic response could be a valuable outcome parameter in neoadj immune checkpoint inhibitor trials.

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1098P Neoadjuvant cytoreductive treatment with BRAF/MEK inhibition of prior unresectable regionally advanced melanoma to allow complete surgical resection, REDUCTOR: A prospective single arm phase II trial

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Background: Approximately 5% of patients with macroscopic regional metastatic melanoma presents with unresectable locally advanced disease. This makes treatment according to standard of care in stage III melanoma, consisting of complete surgical resection and adjuvant systemic therapy, unfeasible.

Methods: In this prospective, single center, single arm phase II trial, 25 patients with BRAF-mutated unresectable stage III melanoma were planned to be included and treated with BRAF and MEK inhibitors dabrafenib (D) 150 mg BID and trametinib (T) 2 mg QD for 8 weeks. If sufficient downsizing occurred, evaluated on PET/CT (week 2 and 8) and by physical examination, patients would proceed to surgery. The primary endpoint was the percentage of patients achieving an R0 resection (tumor free margins) and treatment was considered effective if this was accomplished in at least 8 patients.

Results: Accrual was terminated after inclusion of 21 patients due to achievement of predefined endpoints, slow inclusion rate and changing treatment landscape. All 21 patients completed D+T treatment, of which 2 developed progressive disease after 2 and 8 weeks. The remaining 19 patients proceeded to surgery, of which 17 (81%) achieved an R0 resection. One patient had an R1 resection and in 1 patient no resection was performed due to encasement of vital structures. Pathologic responses were assessed in 18 patients undergoing a resection: 8 (44%) patients had a pathologic complete response (pCR), 8 (44%) a pathologic partial response (pPR) and 2 (11%) showed no pathologic response. At a median follow-up of 43.3 months (IQR 25.9-48.9 months), a median RFS of 9.9 months was seen in patients undergoing surgery. The median OS was not reached. The treatment was well tolerated, with 71% grade 1-2 adverse events (AE), 19% grade 3 AEs. The most commonly reported toxicity was fever (48%).

Conclusions: Neoadjuvant dabrafenib and trametinib shows to be a potent cytoreductive treatment, enabling a radical resection in 17/21 (81%) patients with prior unresectable regionally advanced melanoma.

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1100P Restricted mean survival time (RMST) and cure-rate modeling in estimating survival benefit with adjuvant dabrafenib (D) plus trametinib (T) treatment in melanoma

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Background: Kaplan-Meier and Cox regression time-to-event analyses have traditionally been used to estimate relapse-free survival (RFS) and assess adjuvant treatment effects in high-risk melanoma. However, these methods do not account for nonproportional hazards and/or the potential that a fraction of patients (pts) may never have disease relapse. To overcome these limitations, we evaluated treatment effects using RMST, which assesses area under the survival curve and cure-rate analysis in COMBI-AD.

Methods: COMBI-AD (NCT01682083) is a randomized phase III trial that compared 12 mo of adjuvant D 150 mg twice daily + T 2 mg once daily vs 2 matched placebos (PBO) in pts with resected stage III *BRAF* V600E/K—mutant melanoma, stratified by *BRAF* V600E or K status and disease stage (by AJCC 7 criteria). RMST truncated at 60 mo and a mixed Weibull cure-rate model were used to estimate treatment effect and long-term RFS rates.

Results: Median follow-up was 60 mo and 58 mo in the D+T and PBO arms. At the data cutoff (Nov 8, 2019), RMST across all stages was 41.5 mo (95% CI, 39.4-43.6 mo) with D+T vs 28.7 mo (95% CI, 26.3-31.2 mo) with PBO (representing a gain in RFS of 12.8 mo with D+T over 60 mo). The overall cure rate was 51% (95% CI, 46%-56%) with D+T vs 35% (95% CI, 30%-40%) with PBO, meaning an absolute increase of 16% in the fraction of pts who remain relapse free long term with D+T. RMST and cure rate were improved with D+T across AJCC 7 substages, with the greatest benefit observed in pts with high-risk baseline stage IIIB or IIIC (Table).

Conclusions: RMST and cure-rate models complement conventional statistical methods for 5-year COMBI-AD analysis, demonstrating significant clinical benefit with adjuvant D+T across all stage III substages in pts with melanoma. These analyses may assist oncologists with presenting adjuvant stage III options to their pts.

Table: 1100P RMST at 60 Mo and cure-rate analysis

	Stage IIIA		Stage IIIB		Stage IIIC	
	D+T (n = 83)	PBO (n = 71)	D+T (n = 169)	PBO (n = 187)	D+T (n = 181)	PBO (n = 166)
RMST (95% CI), mo	50.4 (46.7-54.2)	42.2 (36.4-47.9)	41.2 (37.7-44.7)	29.0 (25.4-32.6)	38.0 (34.6-41.3)	22.8 (18.9-26.8)
RMST difference (95% CI), mo	8.2 (1.4-15.1)		12.2 (7.2-17.2)		15.1 (10.0-20.3)	
Cure rate (95% CI), %	63 (49-77)	52 (33-71)	54 (46-62)	33 (26-40)	43 (35-51)	28 (21-36)

Clinical trial identification: COMBI-AD (NCT01682083), conducted in accordance with Study Protocol BRF115532.

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1101P Near real-time intraoperative melanoma diagnosis using deep neural networks

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Background: Intraoperative diagnosis is essential for providing safe and effective care during staged melanoma resections. The existing workflow for intraoperative diagnosis based on H&E staining of processed tissue is time-, resource-, and labor-intensive. Moreover, interpretation of intraoperative histologic images is dependent on a pathology workforce that is contracting and unevenly distributed across the centers where melanoma excisions are performed worldwide.

Methods: We developed an automated workflow that uses deep convolutional neural networks (CNN) to predict diagnosis at the bedside in near real time. Specifically, our CNN, trained retrospectively on over 10,000 H&E images that were collected prospectively across multiple institutions, predicts brain tumor diagnosis in the operating room in under 150 s, which is an order of magnitude faster than conventional techniques.

Results: Our trained CNN was compared to pathologist-confirmed diagnoses in a testing set of 204 patients. Primary endpoint was overall diagnostic accuracy. We show that CNN-based diagnosis of H&E images was noninferior to pathologist-based interpretation of histologic images (overall accuracy, 94.6% vs 95.5%). Additionally, our CNN learned a hierarchy of interpretable histologic feature representations to classify the major histopathologic classes of melanoma. We then developed and implemented a semantic segmentation method that can identify tumor infiltrated and diagnostic regions within the images. Mean intersection over union values was 61 $\pm$ 28.6 for ground truth diagnostic class and 86.0 $\pm$ 28.6 for tumor-infiltrated regions.

Conclusions: We have demonstrated how the application of deep learning can result in near real-time intraoperative melanoma diagnosis. Our workflow provides a means of delivering expert-level intraoperative diagnosis where dermatopathology resources are scarce and improve diagnostic accuracy and efficiency in resource-rich centers.

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1102P Clinical benefit in BRAFV600 mutation-positive melanoma defined by programmed death ligand 1 (PD-L1) and/or lactate dehydrogenase (LDH) status: Exploratory analyses from the IMspire150 study

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Background: The phase III IMspire150 study (NCT02908672) demonstrated that combination therapy with inhibitors of PD-L1 (atezolizumab [A]), BRAF (vemurafenib [V]), and MEK (cobimetinib [C]) improved investigator-assessed PFS vs placebo (P)+V+C (hazard ratio [HR] 0.78; 95% CI 0.63-0.97; log-rank P=0.025). An exploratory analysis was conducted to define efficacy outcomes in key prognostic subgroups defined by baseline PD-L1 and LDH status.

Methods: Treatment-naive patients (pts) with unresectable stage IIIc/IV melanoma (AJCC 7th ed), measurable disease by RECIST 1.1, and $BRAF^{V600}$ mutation–positive tumors were randomized 1:1 to receive A+V+C or P+V+C. PD-L1 expression was assessed using the anti–PD-L1 antibody SP142 (Ventana Medical Systems). PD-L1 status was defined based on the proportion of PD-L1–expressing tumor-infiltrating cells as PD-L1+ (≥1%) or PD-L1– (<1%). LDH levels were defined as high (>ULN) or normal/low (≤ULN).

Results: Treatment benefit, as assessed by PFS and duration of response (DOR), favored the A+V+C arm over the P+V+C arm in all subgroups. Median PFS for A+V+C in the PD-L1– and PD-L1+ subgroups was 15.2 mo and 14.8 mo, respectively, at 18 mo follow-up (Table). In pts with LDH ≤ULN at baseline, PFS and DOR benefit with A+V+C were greater for the PD-L1+ subgroup. Conversely, in pts with LDH >ULN, benefit with A+V+C was greater in the PD-L1– subgroup.

Conclusions: Pts with PD-L1– tumors, which generally benefit less from immunotherapy alone, appear to derive similar clinical benefit from A+V+C as pts with PD-L1+ tumors. This effect was more evident among pts with high LDH levels, which is a known poor prognostic factor in pts with melanoma. Analyses are ongoing to identify other subgroups that may benefit from A+C+V.

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1103P Long-term survival of real-world advanced melanoma patients treated with targeted therapy

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Background: Recent results of patients treated with targeted therapies in clinical trials showed 5-year survival rates of 34% (dabrafenib/trametinib) and 39% (vemurafenib and cobimetinib). This study aimed to investigate the real-world survival of these patients and to identify characteristics of long-term survivors.

Methods: All advanced melanoma patients with a BRAF-V600 mutated tumor who received first-line BRAF-MEK therapy between 2013 and 2017 in the Netherlands were included. Overall survival (OS) was estimated with the Kaplan-Meier method. A multivariable Cox model was used to estimate the association of prognostic factors with OS. Long-term survival was defined as a minimal OS of 2 years from start therapy.

Results: Of 4.282 diagnosed patients, a total of 439 patients received first-line BRAF-MEK therapy. The median OS (mOS) was 11.8 (10.6-13.7) months, and 28% reached 2-year survival. Real-world patients often had symptomatic brain metastases (28%), stage IVm1c disease (87%), ECOG PS ≥2 (20%), ≥3 organ sites (59%), and elevated LDH of ≥250 U/l (31%) and ≥500 U/l (17%). Factors associated with improved survival were age <70 years, stage IIIc, IVm1a or IVm1b disease, normal LDH level, metastases in <3 organ sites, and no brain- or liver metastases. Gender and ECOG PS of ≥1 were not associated with improved survival. Long-term survivors (n=119) had an ECOG PS ≤1 (85%), less stage IVm1c (69%), normal LDH (62%), no brain metastases (78%), no liver metastases (80%) and <3 organ sites (62%). The median treatment duration of BRAF-MEK was 15.5 months. Subsequent immunotherapy was used

Table: 1102P

Subgroup	Median PFS, months, n P+V+C	Median PFS, months, n A+V+C	HR (95%CI)	Median DOR, months, n P+V+C	Median DOR, months, n A+V+C	HR (95%CI)
All	10.6, 258	15.1, 256	0.77 (0.62-0.96)	12.6, 160	21.0, 169	0.68 (0.50-0.91)
PD-L1–	9.2, 86	15.2, 85	0.76 (0.53-1.10)	11.1, 51	19.1, 56	0.78 (0.47-1.30)
PD-L1+	11.4, 158	14.8, 160	0.80 (0.60-1.06)	13.1, 102	22.4, 105	0.59 (0.41-0.87)
PD-L1–, LDH >ULN	5.6, 31	9.8, 27	0.53 (0.29-0.95)	5.2, 15	13.4, 18	0.40 (0.17-0.95)
PD-L1+, LDH >ULN	9.3, 49	6.3, 53	1.16 (0.75-1.80)	12.9, 31	12.9, 27	0.94 (0.49-1.81)
PD-L1–, LDH ≤ULN	11.9, 55	17.8, 58	0.93 (0.58-1.5)	19.5, 36	21.2, 38	0.94 (0.49-1.79)
PD-L1+, LDH ≤ULN	12.9, 109	22.7, 107	0.67 (0.46-0.96)	13.1, 71	N/A, 78	0.53 (0.34-0.85)

in 66% of the long-term survivors, and a complete response occurred in 29%. The mOS of real-world patients treated with first-line BRAF-MEK with characteristics corresponding to the trial eligibility criteria (n=95) was 21.9 (17.3-35.9) months and the 2-year OS was 47%.

Conclusions: Long-term survival of real-world patients treated with first-line BRAF-MEK is significantly lower than of trial patients, mainly due to poorer baseline characteristics of real-world patients. Long-term survivors had more favorable characteristics compared to patients not reaching long-term survival. Based on these 2-year OS results, real-world 5-year survival is expected to be lower than in trials.

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1104P Nivolumab (NIVO) monotherapy or combination therapy with ipilimumab (NIVO+IPI) in advanced melanoma patients with brain metastases: Real-world evidence from the German non-interventional study NICO

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Background: Although melanoma brain metastases (MBM) have a relative incidence of 10%–40% in stage IV disease and often contribute directly to the cause of death, these patients are mostly excluded from prospective clinical studies due to their poor prognoses. Comparatively little is thus known about the effectiveness and tolerability of NIVO and NIVO+IPI in this vulnerable patient population, and real-world evidence for NIVO+IPI, a standard treatment option for MBM, is lacking for first and subsequent lines of therapy.

Methods: NICO is a prospective, observational, multicenter study in Germany associated with ADOREG, assigned to enroll up to 750 patients with advanced melanoma who begin NIVO or NIVO+IPI treatment according to the marketing authorization. Patients will be followed for up to 5 years with assessments performed according to routine clinical practice. The primary objective is overall survival in patients receiving NIVO+IPI. Secondary objectives include overall survival in patients treated with NIVO, progression-free survival, safety profiles, adverse event management, treatment patterns, and patient-reported outcomes.

Results: Of all 623 patients (data cut 30/09/2019) enrolled with advanced melanoma, 64% received NIVO+IPI and 36% NIVO, compared with 74% and 27%, respectively, of patients with MBM (n = 175). NIVO+IPI was preferred over NIVO for patients with more advanced intracranial disease at baseline (MBM, 33.9 vs 21.1%) and who were younger (≤65 years, 62.1 vs 33.9%). For both treatment options, similar fractions of MBM patients were treated in the first (~60%) and subsequent therapy lines (~40%), with better responses for therapy-naïve patients (best overall response rate for NIVO+IPI, 31.0% vs 23.7%; NIVO, 26.9% vs 24%) by trend. The general safety profiles of both immuno-oncology therapies were confirmed. No new safety signals were observed.

Conclusions: We present first real-world data from the second interim analysis of the NICO study in MBM patients treated with NIVO or NIVO+IPI in the first and subsequent treatment lines in routine care in Germany. Overall, both therapies provide effective and safe treatment options.

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1105P Estimating long-term survivorship in patients with advanced melanoma treated with immune-checkpoint inhibitors: Analyses from the phase III CheckMate 067 trial

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Background: Immune-checkpoint inhibitors nivolumab (NIVO) and ipilimumab (IPI), alone and in combination, have demonstrated durable long-term survival patterns in previously untreated patients with advanced melanoma in the CheckMate 067 trial (NCT01844505). Plateaus in overall survival (OS) and progression-free survival (PFS) data can be attributed to survival heterogeneity, which can be better captured by mixture models.

Methods: We assumed that a subset of patients can be classified as long-term survivors (LTSs) and that their survival trend follows that of the general population, with no excess mortality due to melanoma. A cohort-level background survival distribution was derived using mortality rates from the World Health Organization and demographic information from CheckMate 067. After assessing the suitability of mixture models by comparing hazard functions for the 5-year data in the entire trial population and the general population, we fit mixture models to the OS and PFS data to estimate the proportion of LTSs in each treatment arm. Time-to-event outcomes of non-LTSs were modeled by parametric survival functions, the forms of which were varied to obtain a range for the proportions of LTSs and to test the robustness of the results.

Results: Regardless of the data source (OS or PFS), ranges of estimated proportions of LTSs did not overlap across the treatment arms. Based on OS analyses, ranges of estimated proportions of LTSs were 38—46% for NIVO, 49—54% for NIVO+IPI, and 16—26% for IPI. Based on PFS analyses, ranges were 29—33% for NIVO, 38—40% for NIVO+IPI, and 9—13% for IPI. As these ranges represent only a span of point estimates of LTSs across model choices, a formal statistical assessment of the significance of LTSs among the treatment arms would require a comparison of confidence intervals.

Conclusions: Mixture models adequately captured the survival plateaus in CheckMate 067 and suggested a higher proportion of LTSs with NIVO and NIVO+IPI than with IPI. These methods may be used in the indirect estimation of auxiliary outcomes, such as time to subsequent treatment and impact of subsequent treatments on LTSs.

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1106P International experience of ipilimumab and nivolumab in patients with advanced melanoma

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Background: Immune checkpoint inhibition (ICI) combination therapy with ipilimumab (IPI) and nivolumab (NIVO), considered a standard of care for metastatic melanoma, has shown high rates of objective response rate (ORR), progression free survival (PFS) and overall survival (OS), but at a cost of significant toxicity. We aimed to analyse the efficacy and toxicity outcomes related to treatment with IPI and NIVO in routine practice in a multicentre cohort of patients (pts) with metastatic melanoma.

Methods: We conducted a retrospective review of medical notes of pts with advanced melanoma (unresectable Stage 3 or Stage 4) treated with IPI and NIVO between 2015 and 2020 at 6 centers across Europe, USA and Australia. Baseline characteristics were collected including the presence of brain metastases (BM). The primary endpoint was OS in the non-BM cohort. Secondary endpoints were PFS, ORR and immune-related adverse events (irAE) in the whole cohort and BM pts only.

Results: 696 pts with median follow-up of 13 months (m) were included. Median age was 58 years, 400 (57%) were male, 678 (97%) had PS- ECOG 0-1. Primary site was cutaneous in 487 pts (70%), unknown in 133 pts (20%) and other (acral, mucosal and uveal) in 77 pts (10%). 352 pts (50.5%) had a BRAF mutation, 516 pts (74%) were treatment naive, 241 pts (35%) had BM, of which 131 (18%) were untreated. 277 pts (40%) had elevated LDH. ORR was 48% (95% CI, 45-52). Median PFS (mPFS) was 6m (95% CI, 4.3-7.6), median OS (mOS) was 38m (95% CI, 26.6-49.3) for the entire cohort. mOS in non-BM pts was 52 m (95% CI, NR-NR) and 14m (95% 5-23) in BM pts. Intracranial (IC) ORR was 43% (95% CI, 37-49) and IC disease-control-rate was 56% (95% CI, 49-62). 253 pts (36%) started maintenance NIVO. Any irAE occurred in 76% of pts; grade 3/4 in 44%, hospital admission rate was 36%, and 4 (0.7%) treatment-related deaths (1 pneumonitis, 2 myocarditis and 1 colitis) were recorded.

Conclusions: The findings on this large cohort of pts support efficacy and provide insights into pts characteristics and outcomes associated with IPI and NIVO treatment for a heterogeneous population with advanced melanoma and are comparable with those of previously reported pivotal trial, Checkmate 067. Further analysis of the data including prognostic factors is ongoing.

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1107P Clinical outcomes to checkpoint inhibitors in NRAS mutated metastatic melanoma (MM) compared with wild type BRAF/NRAS: An Italian Melanoma Intergroup (IMI) study

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Background: At present, the standard treatment for NRAS mutated MM is the same as for BRAF wild type MM with immune checkpoint inhibitors (ICIs) used as first line. It is thought that NRAS mutation is associated with better outcomes to immunotherapy. Nevertheless, retrospective studies reported controversial findings. To better understand the predictive role of NRAS mutation to ICIs, we assessed retrospectively clinical outcomes in two cohorts of pts homogeneously treated with ICIs as first line therapy: NRAS mutated/BRAF wild type MM (mut/wt) and NRAS wild/BRAF wild type MM (wt/wt).

Methods: A total of 331 pts including 163 mut/wt and 168 wt/wt were recruited in 11 Centres in Italy. The main evaluated pts features included: sex, age, origin and characteristics of primary cancer, previous adjuvant therapy, ECOG PS, M stage, metastatic sites, lactate dehydrogenase (LDH) level, basal count of white blood cells, lymphocyte and platelet, and subsequent therapies. In the wt/wt population, 35 pts received ipilimumab, 131 antiPD-1or antiPD-L1 and 2 the combination of both. In the cohort mut/wt, 45 patients received ipilimumab, 115 antiPD-1 and 3 the combination.

Results: As regard the primary, mut/wt was more frequently ulcerated (p.0038) and arose more frequently on the trunk (p.003) with respect wt/wt. At the onset of advanced stages, mut/wt had a higher M1c rate (p.001) involving less frequently lung (p.007) and brain (p.011) and progressing less to the brain if case be so (p.011). There was no significant difference in ORR, PFS and OS between the two groups (41.4%, 11 months [6-20, 95% CI] and 32 months [23-61, 95% CI] in mut/wt and 36,1%, 9 months [6-17, 95% CI] and 27 months [16-35, 95% CI] in wt/wt). Univariate analysis across the entire population showed a better ORR significatively associated with normal LDH, <3 sites of metastases, N/L ratio under 2.5 and the use of antiPD-1 than antiCTLA-4. A longer PFS and OS were also correlated with normal LDH, <3 sites of metastases, N/L ratio $<2,5$, lower platelet count and the use of antiPD-1 than antiCTLA-4.

Conclusions: We provide evidence that ICIs used as first line therapy are equally effective in mut/wt and wt/wt MM.

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1108P Real world (RW) sequencing outcomes with immunotherapy and targeted therapy (TT) in BRAF+ metastatic melanoma (The NOBLE study series)

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Background: Initial treatment decision-making for BRAF+ Metastatic Melanoma (MM) patients remains complex. TT with BRAF-MEK inhibition is associated with high ORR but are thought to be of limited duration, while checkpoint inhibitors (IO) are associated with lower ORR but can be more durable. In absence of head-to-head clinical trial data, it is unclear which treatment sequence (1L IO to 2L TT vs 1L TT to 2L IO) provides maximum benefit to patients. This study compares outcomes in the RW across the two treatment sequences.

Methods: The study included BRAF+ MM patients (n=358) who received both 1L and 2L therapies (IO and TT) according to the NCCN guidelines from Jan 1, 2014 up to Dec 31, 2018. Data was obtained from academic and community sites in the US using a RW registry (NOBLE study). Patient characteristics were analyzed descriptively. Kaplan-Meier curves and Cox regression model were used to compare progression free survival (PFS) and 2-year overall survival (OS) across the two treatment sequences. Differences in patient characteristics including disease severity across the two sequences were adjusted using inverse probability of treatment weighting (IPTW).

Results: Patients who received the TT to IO sequence vs IO to TT sequence were more likely to have elevated LDH (30.2% vs 17.7%) and 3+ organ sites of metastasis (47.4% vs 36.5%). Regardless of treatment sequence, patients progressed relatively rapidly through both 1L and 2L therapies (combined PFS of 13.2m for TT-IO and 12m for IO-TT). The 2-year OS was 76% for the TT-IO sequence compared to 77% for IO-TT. Adjusted Cox regression model found no statistical difference in outcomes across the two sequences.

Conclusions: RW data suggests that half of BRAF+ MM patients, regardless of initial treatment choice, are likely to progress through both 1L and 2L treatments within 12 months. Pending the results of randomized clinical trials, this RW study found no

difference in outcomes across treatment sequences. BRAF+ MM patients may require more intensive, alternative approaches than the current sequential TT/IO approach, as outcomes in clinical practice are suboptimal.

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1109P Chinese subgroup results from an open-label, phase IIa study of dabrafenib plus trametinib in Asian patients with advanced BRAF V600-mutant melanoma (NCT02083354)

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Background: Dabrafenib plus trametinib has approved for BRAF V600−mutant unresectable or metastatic melanoma on the basis of results from the COMBI-d and COMBI-v trials. However, there is limited data of the combination in Asian populations. NCT02083354 is a single-arm, open-label, multicenter, phase IIa study in 77 Asian patients with stage III and IV *BRAF* V600−mutant melanoma. Here we report the efficacy results of the Chinese subgroup in this study.

Methods: Enrolled patients were diagnosed unresectable or metastatic BRAF V600 mutant melanoma, non-treated or pretreated, but no prior treatment with BRAF or MEK inhibitors. Patients were assigned to receive dabrafenib 150 mg q12h and trametinib 2 mg once daily. Primary endpoint was the ORR by investigator assessment using RECIST v1.1. Secondary endpoints included PFS, duration of response and OS.

Results: Between March 2014 and November 2017, 61 Chinese patients enrolled in NCT02083354 trial (1 patient withdraw consent after enrollment). The ORR was 71.7%, and the complete response was observed in 4(6.7%) patients. 39(65%) patients had partial responses, and 17 (28.3%) patients had stable diseases. ORR was 86.7% in treatment naive patients (n=15). ORR of patients previously received chemotherapy (n=43) was 65.1% and that of patients previously received PD-1 inhibitor (n=7) was 85.7%. The median PFS was 9.33 month (95% CI, 7.87-10.78 and 11.2 months in ITT and treatment naive population, respectively. Median OS was 21.1 month (95%CI, 16.6-25.7) and 24 months in ITT and treatment naive population, respectively. Particularly, the ORR, PFS and OS was 88.9%, 7.47 months and 21.4 months respectively in acral melanoma (n=12), showing no statistically significance with that of non-acral patients.

Conclusions: This analysis demonstrates meaningful efficacy of dabrafenib plus trametinib in Chinese patients with advanced BRAF V600 mutant melanoma, including acral melanoma patients.

Table: 1109P

Characteristics	Patients (n = 60)
Age (years)	48.75±12.27
Male, n (%)	24 (40%)
Clinical subtype of primary site	
Non-CSD	24 (40.0%)
CSD	15 (25.0%)
Acral	12 (20.0%)
unknown	9 (15.0%)
Tumor stage at screening, n (%)	
Unresectable stage IIIc	2 (3.3%)
Stage IV	
M1a	10 (16.7%)
M1b	14 (23.3%)
M1c	31 (51.7%)
Unknown	3 (5%)
LDH, n (%)	
≤ULN	37 (61.7%)
>ULN	23 (38.3%)
Number of prior therapies, n (%)	
0	15 (25%)
1	19 (31.7%)
2	19 (31.7%)
≥ 3	7 (11.7%)
Prior immunotherapy, n (%)	9 (15%)
Number of metastatic organs, n (%)	
1	12 (20%)
2	13 (21.7%)
≥3	35 (58.3%)

Legal entity responsible for the study: Novartis.

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Disclosure: All authors have declared no conflicts of interest.

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1110P Efficacy of salvage therapies after failure of anti-PD-1 monotherapy for advanced melanoma in an Asian population: A multi-institutional historical cohort study

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Background: Anti-programmed cell death protein 1 monotherapy (PD1) leads to a favorable response in approximately 40% of advanced melanoma cases among Caucasian populations; however, two-thirds of patients (pts) show innate or acquired resistance to PD1, subsequently requiring salvage therapy. Moreover, the clinical efficacy of PD1 is lower in Asian populations. Although the potential benefits of salvage therapies after PD1 failure, including BRAF inhibitor plus MEK inhibitor (BRAFi/MEKi) and nivolumab plus ipilimumab (nivo/ipi), are being elucidated in Caucasian populations, little is known about these benefits in Asian populations. We investigated the efficacy of salvage systemic therapies in Japanese pts with melanoma after PD1 failure.

Methods: Japanese pts with advanced melanoma after PD1 failure who then proceeded to salvage systemic therapies were included from 21 Japanese institutions. The inclusion criteria were as follows: 1) ipilimumab-naive pts, 2) any line of BRAFi/MEKi, and 3) consecutive systemic therapy initiated within 2 months after PD1 failure. The primary outcome was the objective response rate (ORR), while the secondary outcomes were progression-free survival (PFS) and overall survival (OS).

Results: In total, 245 pts were included; 53.5% of the pts received ipilimumab, 15.1% received nivo/ipi, 12.2% received BRAFi/MEKi, and the remaining received cytotoxic chemotherapies as salvage therapy. BRAFi/MEKi demonstrated an ORR of 40%, significantly higher than those of ipilimumab (9.9%, P<0.001), nivo/ipi (13.5%, P=0.02), and cytotoxic chemotherapy (14.9%, P=0.02). No significant difference was observed between the ORRs of ipilimumab and nivo/ipi (P=0.55). BRAFi/MEKi also showed prolonged PFS than those of other systemic therapies (P=0.001); however, there was no significant difference between the OS of the salvage therapies (P=0.54). No significant differences were also observed between the survival of ipilimumab and nivo/ipi (PFS, P=0.29; OS, P>0.99).

Conclusions: Unlike in Caucasian populations, salvage nivo/ipi shows limited efficacy in Japanese pts, which is similar to that of ipilimumab after PD1resistance, although longer follow-up is needed in nivo/ipi arm. BRAFi/MEKi appears to be favorable compared with other regimens for BRAF-mutated melanoma.

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1111P Suboptimal real-world (RW) outcomes for BRAF+ metastatic melanoma (MM) patients in 2L therapy (The NOBLE study series)

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Background: Targeted Therapy (TT) and immuno-oncology (IO) based therapy have each demonstrated significant clinical benefits when used in 1L for BRAF+ MM patients. However, there is very limited data available on characteristics and outcomes once MM patients progress on 1L treatment. To address this data gap, this study examined real-world disease severity, progression free survival (PFS) and overall survival (OS) outcomes in BRAF+ MM patients receiving 2L therapy and compared them to outcomes observed in 1L.

Methods: The study included RW BRAF+ MM patients who received 1L (n=1010) and 2L (n=358) IO or TT therapy according to NCCN guidelines from Jan 1, 2014 up to Dec 31, 2018. Data was abstracted from >150 academic and community sites in the US (NOBLE study). Patient characteristics at the time of initiation of 1L and 2L were compared descriptively. Kaplan-Meier survival curves were used to compare rwPFS and OS in both 1L and 2L settings.

Results: At 1L initiation, 68% of RW patients met criteria for high tumor burden (high LDH and/or 3+ organ sites of metastasis). Median PFS following 1L therapy was 6.4 months in this RW patient population. Upon 2L initiation, increase in disease severity was observed and 47% of patients had developed new sites of metastases. The median rwPFS dropped by 30% in 2L therapy to 4.6 months. The mortality rate nearly doubles in the patients requiring two lines of therapy (21%) vs patients requiring 1 line of therapy (12%) within the 1st year.

Table: 1111P

Time	First line		Second line	
	Progression rate	Median PFS	Progression rate	Median PFS
6 months	50%	6.4 months	58%	4.6 months
1 year	64%		75%	
2 years	75%		87%	

Conclusions: This RW analysis of BRAF+ MM patients demonstrates poor PFS and mortality estimates for those patients requiring a second line of therapy. Consideration should be given to identifying patients that may benefit from more intensive treatment upfront to maximize clinical benefit in 1L and delay patients' transition to 2L. Further study and analyses are warranted to best understand RW outcomes as therapies in MM continue to evolve.

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1112P Intralesional therapy with talimogene laherparepvec for stage IIIB-IVM1a melanoma is able to achieve a high rate of complete and durable responses and is associated with tumour load

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Background: Talimogene laherparepvec (T-VEC) is a genetically modified herpes simplex type 1 virus and known as an effective oncolytic immunotherapy for injectable cutaneous, subcutaneous and nodal melanoma lesions in stage IIIB-IVM1a patients, as approved by the European Medicines Agency (EMA). The objective of the current study was to identify prognostic factors for achieving a complete response (CR) that can be used to select patients for treatment with T-VEC monotherapy.

Methods: Patients with stage IIIB-IVM1a melanoma, treated with T-VEC at the Netherlands Cancer Institute between 2016-12 and 2019-05 with a follow-up time > 6 months, were included. Data was collected on baseline characteristics, responses and adverse events (AEs). Uni- and multivariable analyses were conducted and a prediction model was developed to identify prognostic factors associated with CR.

Results: A total of 71 patients were included with a median age of 68 years (range: 35-90). The median follow-up time was 16.1 months. As best response, 47 patients (66%) had a CR and 10 patients (14%) had a PR, resulting in an overall response rate of 80%. Twenty-one patients (30%) stopped treatment because of progressive disease and 16 patients (32%) developed a recurrence during follow-up after achieving a PR or CR. Median duration of CR was 11 months. The durable response rate (objective response lasting continuously > 6 months) was 42%. Grade 1-2 AEs occurred in almost every patient. Tumor size, type of metastases, prior treatment with systemic therapy and stage (8Th AJCC) were independent prognostic factors for achieving a CR. The prediction model includes the predictors tumor size, type of metastases (only cutaneous vs. subcutaneous (+/- cutaneous) vs. nodal (+/- cutaneous/subcutaneous)) and number of lesions.

Conclusions: This study shows that intralesional T-VEC monotherapy for stage IIIB-IVM1a melanoma is able to achieve high complete and durable response rates. The prediction model shows that use of T-VEC in patients with less tumor burden is associated with better outcomes, suggesting T-VEC should perhaps be used earlier in the course of the disease.

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1113P Mortality prediction in real world advanced melanoma patients treated by anti-PD1 within MelBase, a French multicentric prospective cohort

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Background: Anti-PD1 (Nivolumab, Pembrolizumab, APD) treatment (monotherapy or combination) efficacy is largely documented in advanced melanoma (AM) patients, as well as classical prognostic factors for longer survival. This study investigates 1- and 2-years mortality prediction in real world AM patients (rwAM), according to the most associated prognostic factors.

Methods: Clinical characteristics were collected from MelBase, a French multicentric biobank prospectively enrolling unresectable stage III or IV melanoma (26 centers, >1900 patients, NCT02828202). Data from 793 patients treated by APD in monotherapy (47% in 1st line in May 2019) were collected. Data were analyzed to develop a risk prediction model for 1- and 2-years overall survival (OS) in rwAM patients, using Random Forests. Performance was expressed in terms of calibration and discrimination (c-statistic). Model internal validation was performed by computing out-of-bag prediction error of Random Forests.

Results: Median age was 65 years, 92% of patients were ECOG 0-1, 36% BRAF mutated, 37% had elevated LDH, 55% were M1c (AJCC 7th edition), 26% had hepatic metastases and 41% had more than 3 metastatic organ sites (MOS). Among the 793 patients, 41% were treatef by nivolumab and 59% by pembrolizumab.

Median follow-up was 14 months (Q1-Q3 6-25) and median OS 19 months (95%CI 17 -24). The mortality risk score we developed used LDH, ECOG, BRAF, >3 MOS and the presence of hepatic metastasis at treatment initiation. It showed a fair discrimination, with a C statistic of 0.73 (95% CI 0.72-0.75) for 1-yr OS and 0.71 (0.70-0.74) for 2-yr OS. Out-of-bag prediction error was low, with values of 0.05 for 1-yr OS and 0.06 for 2-yr OS.

Model recalibration was necessary, due to overestimation of low mortality. After log transformation, the calibration curves indicated that the model was well calibrated and no deviation from the reference line.

Conclusions: This study predicts medium term survival (12, 24 months) according to baseline characteristics for rwAM patients treated by APD1 in monotherapy.

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1114P A real-world study of vemurafenib plus anti-PD-1 antibody in Chinese patients with advanced BRAF V600-mutant melanoma

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Background: Preclinical data suggest that BRAF inhibition provides a more favorable immune microenvironment for subsequent response to immunotherapy. We aimed to evaluate the efficacy and safety of combining vemurafenib (BRAF inhibitor) with a programmed death 1 (PD-1) inhibitor in patients with *BRAF*^{V600}-mutant melanoma in China.

Methods: Advanced *BRAF*^{V600}-mutant melanoma patients treated with vemurafenib and anti-PD-1 antibody at Sun-Yat Sen University Cancer Center between June 2017 and May 2019 were retrospectively analyzed. Vemurafenib was administered with a 4—6-weeks run-in period followed by PD-1 blockade (pembrolizumab or toripalimab) combined with vemurafenib until disease progression or unacceptable toxicity. Response was assessed by the Response Evaluation Criteria in Solid Tumors version 1.1.

Results: In total, 39 patients were included. All the patients had tumor shrinkage. The objective response rate was 64.1% (95% CI, 48.7—79.4) and the complete response was observed in 8 (20.5%; 95% CI, 7.7—33.3) patients. The median progression-free survival (PFS) was 13.2 months (95% CI: 8.2—18.2). The median duration of response (DOR), and overall survival (OS) were not reached after a median follow-up of 12.1 months. The response was ongoing in 16 (41%) patients. The estimated 1-year survival rate was 86.7%. During the combination therapy, treatment-related adverse events (TRAEs) of any grade occurred in 36 (92.3%) patients. Eleven patients (28.2%) experienced grade 3/4 TRAEs, 10 presented with rash and 1 with elevated transaminase. TRAEs led to discontinuation of ≥1 study drug in seven (17.9%) patients. Programmed death ligand 1 expression on the tumor cell and tumor mutation burden at baseline did not correlate with response rate and survival time.

Table: 1114P

Characteristic	No. of patients (%), n = 39
Age, years	51 (24—77)
Male	26 (66.7)
ECOG	
0	22 (56.7)
1	17 (43.6)
Clinical subtype of primary tumor	
Acral	2 (5.1)
CSD	11 (28.2)
Non-CSD	19 (48.7)
Unknown	7 (17.9)
Brain metastases	
Yes	6 (15.4)
No	33 (84.6)
Liver metastases	
Yes	11 (28.2)
No	28 (71.8)
Metastatic organs	
>2	17 (43.6)
≤2	22 (56.4)
LDH	
≤UNL	30 (76.9)
> UNL	9 (23.1)
Prior systemic therapy	
No	29 (74.4)
Yes	10 (25.6)

Conclusions: Vemurafenib combined with anti-PD-1 antibody had promising clinical activity and manageable safety. Toxicity, especially rash, is more common for this combination than for either agent alone.

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1115P Association between hospital stays with infection and overall survival in patients treated with ipilimumab, analysis of the French nationwide exhaustive hospital discharge database (PMSI)

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Background: Recent development of immune checkpoint inhibitors (ICI) has revolutionized cancer management. Antibiotics can significantly disrupt the composition of the gut microbiota. This microenvironment plays a key role in the regulation of the immune system. Its modification could affect the efficacy of ICI. We aimed to assess the association between hospital stays with infection and overall survival in patients (pts) treated with ipilimumab.

Methods: All pts treated with ipilimumab between January 2012 and December 2014 were selected from the PMSI national database. Antibiotic exposure was defined as the presence of a hospital stay with an infection during the 2 months prior to the first course of ipilimumab (C1) or within the following month. The primary outcome, overall survival (OS) was defined as the time interval between C1 and date of death; data were censored at the last hospital stay for patients without reported death. OS was estimated by Kaplan-Meier method and compared by the log-rank test and by Cox regression models.

Results: We studied 44357 hospital stays from 97 centres, involving 1661 pts (1072 in 2014). Our data appear to be complete: French National Cancer Institute (INCA) lists 1080 pts in 2014. All pts received ipilimumab as monotherapy for an advanced melanoma. Overall, 123 of the 1661 (7.4%) pts were considered as receiving antibiotics in hospital during the exposure defined period. The most frequent sites of infection were: skin (21.6%), respiratory tract (20.4%) and digestive system (14.4%). Infection was associated with a shorter OS: median 6.3 versus 15.4 months, hazard ratio, HR=1.91; 95% confidence interval (CI) 1.48-2.46, $p=10^{-6}$. In multivariate analysis adjusted for covariates, the association between infection and OS remained significant: HR=1.71; 95%CI, 1.32-2.21, $p=10^{-5}$; malnutrition and brain metastases were also significantly associated with poor OS: HR=4.37; $p=10^{-13}$; and HR=1.90; $p=10^{-11}$, respectively.

Conclusions: Infection and antibiotic administration in hospital around the first course of ipilimumab appear to be associated with a significant reduction in clinical benefit from ipilimumab in advanced melanoma.

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1116P Real-world clinical outcomes with pembrolizumab (pembro) for treatment of advanced melanoma: Evidence from the United States community oncology setting

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Background: Clinical trials have demonstrated improved overall survival (OS) and progression-free survival (PFS) associated with pembro for treatment of advanced melanoma. As real-world data availability differs from trials, this study assessed OS, as well as proxies for PFS based on provider-documented response assessments.

Methods: Adult patients (pts) with advanced melanoma who initiated pembro between 01 January 2014 – 31 December 2016 were followed through 01 January 2020 (18.2 months median follow-up). Study data were sourced through electronic health records. Kaplan-Meier (KM) methods were used to assess: OS, time to treatment discontinuation (TTD), time to next treatment (TTNT), time to physician-assessed tumor progression (rwTTP) and physician-assessed PFS (rwPFS) from initiation of pembro, with log-rank tests to assess differences by line of therapy. Multivariable Cox regression models were constructed to evaluate independent risk factors for OS and rwPFS.

Results: 303 pts were included (median age 67 years, 94.4% Caucasian, 63.0% male): 119, 131 and 53 received pembro in the first- (1L), second- (2L) and third-line or beyond (3L+) setting, respectively. The table presents the KM estimates (in months) of clinical outcomes. Increased age and worsening performance status were associated with an increased risk of all-cause death, while elevated lactate dehydrogenase, brain metastases and 3L+ pembro were associated with both an increased risk of all-cause death as well as progression or death.

Conclusions: Favorable clinical outcomes were associated with pembro, especially in the 1L setting. Similar median durations of TTD and rwPFS were observed, with markedly higher estimates observed for TTNT and rwTTP.

Legal entity responsible for the study: McKesson Life Sciences.

Funding: Merck & Co.

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1117P Immunotherapy in octogenarian and nonagenarian metastatic melanoma patients

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Background: Immunotherapy with anti-programmed cell death-1 (PD-1) agents is an effective treatment for metastatic melanoma. Research indicates that the response to treatment with anti-PD-1 in patients over 65 years of age is better. Octogenarian and nonagenarian represent a significant proportion of patients and are a clinical challenge.

Table: 1116P

Endpoint (in months; 95% confidence interval)	Overall	1L	2L	3L+	Log-rank p-value
OS	29.3(20.3,49.7)	42.8(24.8,NR)	30.0(14.9,54.5)	13.8(4.8,25.7)	0.0080
TTD	4.8(3.6,5.3)	5.1(4.0,8.1)	4.8(3.5,6.0)	2.8(1.4,6.2)	0.7118
TTNT	10.6(7.3,18.8)	19.5(8.5,27.3)	8.9(5.6,18.8)	6.5(3.7,19.0)	0.2615
rwTTP	11.2(6.7,20.7)	18.2(8.5,43.2)	13.1(4.4,37.1)	3.4(2.1,16.4)	0.1875
rwPFS	5.1(4.0,7.6)	8.1(4.6,14.4)	5.1(3.6,13.1)	2.8(1.4,4.8)	0.0193

NR, not reached.

Methods: Our multicenter retrospective analysis included 499 patients treated with anti-PD-1 agents (nivolumab or pembrolizumab) between 2017 and 2019. 208 patients were aged <65 years, 218 patients were aged 65-79 years, and 73 patients were aged 80-100 years. We analysed the efficacy and toxicity of anti-PD-1 therapy at the age of 80-100 years compared to the age of 65-79 years and to <65 years. Baseline parameters, response rate (overall response rate -ORR), best response, progression-free survival (PFS), *melanoma-specific survival* (MSS) and immune-related adverse events were analysed. The Kaplan–Meier method was used to estimate PFS and MSS, Cox regression, t test, and chi-square test were used for statistical analysis.

Results: Baseline parameters were comparable. There was no statistically significant difference between the groups aged <65 years, aged 65-79 years and aged 80-100 years of MSS (p=0.2781), PFS (p=0.5373), the number of responses to treatment (p=0.155) and the occurrence of irAE (p= 0.821). In the multivariate analysis, the presence of brain metastases, elevated LDH levels, and the occurrence of at least one irAE had a statistically significant impact on OS and PFS. The age, gender, *BRAF* mutation, primary lesion location, type of anti-PD-1 therapy had no statistically significant effect on MSS and PFS in the multivariate analysis. Toxicity for all groups was similar. Immune related adverse events in grade 3 or 4 were reported in 5%, 5.5% and 4% of patients in the groups aged <65 years, aged 65-79 years and aged 80-100 years, respectively.

Conclusions: Anti PD-1 therapy in octogenarian and nonagenarian metastatic melanoma patients has similar efficacy and toxicity compared to patients aged <65 years and 65-79 years. The patient's age cannot be the reason for disqualification from anti-PD-1 treatment.

Legal entity responsible for the study: Bożena Cybulska-Stopa.

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1118P Retrospective analysis of safety in elderly BRAF V600 mutation-positive advanced melanoma patients treated with dabrafenib (D) and trametinib (T) and correlation with non-elderly patients

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Background: Melanoma in elderly patients has different features, and this population has higher risk of comorbidities. Efficacy and safety of D+T have been well established in 2 clinical phase III trials, however limited data has been reported for the elderly population. This study analyzes the real world care of patients with advanced melanoma treated with D+T in Spain, focused on the elderly population.

Methods: We performed a retrospective descriptive analysis of elderly (≥75 years old, y.o.) and non-elderly (<75y.o.) BRAFV600+ advanced melanoma patients treated with D+T or D monotherapy in 10 Spanish academic centers. Clinical variables, safety, and efficacy of both groups were compared. Influence of variables on the initial dose and safety was analyzed by univariate and multivariate analysis.

Results: 159 patients were included, 130 <75y.o. and 29 ≥75y.o. Clinical features were similar between groups, except in number of comorbidities, number of metastatic sites, ECOG-PS, and BRAFV600 mutation type. 5 patients per group received D monotherapy (p=0.019) and this decision was only influenced by age. There were no differences in adverse events (AE) rate or grade between groups. However, pyrexia was more frequent in patients <75y.o. (42.3% vs 13.8%, p=0.005) while asthenia was more frequent in the elderly group (44.8% vs 25.4%, p=0.044). Besides, AE management was different: 83.5% of AEs in <75 y.o were treated without D or T modifications vs 64.5% in the elderly (p<0.001). Overall, ≥75y.o. patients had more D dose modifications (22.3 vs 41.4%, p=0.039), lower initial dose of T (p=0.005), more T interruptions (26.4 vs 50%; p=0.029) and less D and T dose intensity (p=0.018 and p=0.020). There were no differences in efficacy between groups, with a response rate, median progression-free survival and overall survival of 63.8%, 8.6 and 22.3 months in <75y.o. vs 62%, 10.3 and 29.1 months in ≥75 y.o.

Conclusions: D+T is safe and effective in ≥75 y.o. patients with advanced BRAF600+ melanoma. AE management is different in this population compared to <75 y.o. patients. Differences in AE profile as the lower rate of pyrexia in elderly patients should be confirmed in future studies.

Legal entity responsible for the study: Novartis.

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Disclosure: A. García-Castaño: Advisory/Consultancy, Speaker Bureau/Expert testimony: Pierre-Fabre; Advisory/Consultancy, Speaker Bureau/Expert testimony: Novartis; Advisory/Consultancy, Speaker Bureau/Expert testimony: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony: Bristol-Myers Squibb; Advisory/Consultancy, Speaker Bureau/Expert testimony: Merck Sharp & Dohme; Advisory/Consultancy, Speaker Bureau/Expert testimony: Sanofi; Advisory/Consultancy, Speaker Bureau/Expert testimony: Merck. I. González-Barrallo: Advisory/Consultancy: Novartis; Advisory/Consultancy: Bristol-Myers Squibb; Research grant/Funding (institution), Clinical trial costs: Merck Sharp & Dohme. J. Medina Martínez: Advisory/Consultancy, Travel/Accommodation/Expenses: Novartis; Advisory/Consultancy, Travel/Accommodation/Expenses: Roche; Advisory/Consultancy, Travel/Accommodation/Expenses: Bristol-Myers Squibb; Travel/Accommodation/Expenses: Merck Sharp & Dohme. J.L. Manzano Mozo: Advisory/Consultancy: Bristol-Myers Squibb; Advisory/Consultancy: Novartis; Advisory/Consultancy: Pierre-Fabre; Advisory/Consultancy: Roche; Advisory/Consultancy: Merck Sharp & Dohme; Advisory/Consultancy: Amgen; Advisory/Consultancy: Merck. M. Majem Tarruella: Advisory/Consultancy, Research grant/Funding (institution): Bristol-Myers Squibb; Advisory/Consultancy, Non-remunerated activity/ies: Merck Sharp & Dohme; Advisory/Consultancy, Non-remunerated activity/ies: Boehringer Ingelheim; Advisory/Consultancy, Non-remunerated activity/ies: AstraZeneca; Advisory/Consultancy, Non-remunerated activity/ies: Roche; Advisory/Consultancy: Kyowa Kyrin; Advisory/Consultancy: Pierre-Fabre. C. Aguado de La Rosa: Advisory/Consultancy, Non-remunerated activity/ies: Roche; Advisory/Consultancy: AstraZeneca; Advisory/Consultancy: Boehringer Ingelheim; Advisory/Consultancy: Sanofi; Non-remunerated activity/ies: Novartis; Advisory/Consultancy: Pierre-Fabre; Advisory/Consultancy: Merck Sharp & Dohme; Advisory/Consultancy: Bristol-Myers Squibb. I. Palacio: Advisory/Consultancy, Travel/Accommodation/Expenses: Novartis; Advisory/Consultancy, Travel/Accommodation/Expenses: Roche; Advisory/Consultancy, Travel/Accommodation/Expenses: Merck Sharp & Dohme; Advisory/Consultancy, Travel/Accommodation/Expenses: GlaxoSmithKline. L. Osterloh: Full/Part-time employment: Novartis. A. Martinez Fernandez: Full/Part-time employment: Novartis. All other authors have declared no conflicts of interest.

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1119P Targeted treatment and immunotherapy in older patients with advanced melanoma: A single institution real-life experience

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Background: Malignant Melanoma (MM) is associated with poor prognosis in advanced stages and a rising incidence with age. We aim to provide real-life data on targeted therapy (TT) and anti-PD1 safety profile in older MM patients (pts).

Methods: Retrospective cohort of all consecutive pts ≥ 65 years old (yo) with advanced MM (excluding uveal and mucosal) who started TT or anti-PD1 between Apr'14 and Dec'19 in a Portuguese cancer centre. Data were collected from retrospective chart review: baseline characteristics, primary outcome – safety profile (adverse events [AE], grading by CTCAEv5, and dose reduction or discontinuation due to toxicity). Descriptive analysis performed using frequencies for categorical variables and median and range for continuous variables.

Results: We identified 120 pts, 53% male, median age 76.4 yo (range, 65.3-93.3), 80% with ECOG PS 0-1, 91% cutaneous origin, 50% with LDH > ULN, and 18% had brain metastases at baseline. We treated 53 pts (15 pts ≥ 80 yo) with TT: 9 with vemurafenib (V) - 7 1stline; 12 with vemurafenib/cobimetinib (V+C) and 32 with dabrafenib/trametinib (D+T), all 1stline. Seventy-two pts (23 pts ≥ 80yo) received anti-PD1 (pembrolizumab, nivolumab): 64 1stline, 6 2ndline (5 pts after TT, 1 pt after dacarbazine) and 2 3rdline (after dacarbazine and ipilimumab). Ninety-two percent was BRAF wildtype. Most frequent AE (any grade) with TT: rash (89%), photosensitivity (67%) and arthralgia (67%) with V; increased creatinine (58%), increased aminotransferases (50%) and nausea (50%) with V+C; fever (53%), nausea (34%) and fatigue (28%) with D+T. Grade 3-4 in 41% of all pts and 60% of pts ≥ 80 yo. Dose reduction in 53% and discontinuation in 17% of all pts. Most frequent AE (any grade) with anti-PD1: fatigue (46%), pruritus (18%), and hypothyroidism (17%). Grade 3-4 in 15% of all pts and 17% of pts ≥ 80 yo. Discontinuation in 15% of all pts. No toxic deaths were found.

Conclusions: Our findings do not show increased incidence of AE in the elderly in a real-life setting as compared topivotal clinical trials. Despite the possibility of under-reporting of AE due to the study design, these findings suggest that age itself should not limit the use of these drugs. Predictive tools of toxicity in this population are needed.

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1120P Post-approval trials versus patient registries: Comparability of advanced melanoma patients with brain metastases

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Background: Post-approval trials and patient registries have their pros and cons in generating post-approval data for medicine evaluation. No direct comparison between these post-approval data sources yet exists for advanced melanoma patients. We compared outcomes of patients with brain metastases (BM) treated with targeted therapies in post-approval trials with outcomes from a population-based patient registry. We aimed to explore whether a patient registry can complement or sometimes even replace post-approval trials.

Methods: Post-approval single-arm clinical trial data and real-world data from the Dutch Melanoma Treatment Registry (DMTR) were used. The study population consisted of patients with BM treated with targeted therapies (BRAF- or BRAF-MEK) in the first line. Two models were used to compare the data sources: a Cox hazard regression model and Propensity Score Matching (PSM).

Results: Four single-arm post-approval clinical trials on patients with advanced melanoma and BM were pooled, resulting in 467 patients. Real-world patients (n=602) had statistically significantly higher age, higher ECOG PS, more often metastases in ≥3 organ sites, and more often symptomatic BM than patients treated in post-approval trials. Lactate dehydrogenase (LDH) levels were similar. The unadjusted median overall survival (mOS) of post-approval clinical trial patients was 8.7 (95%CI; 8.1-10.4) months compared to 7.2 (95%CI; 6.5-7.7) months ($p<0.01$) for real-world patients. With the Cox model, survival was adjusted for prognostic factors, leading to a statistically insignificant difference in mOS of respectively 8.7 (95%CI; 7.9-10.4) compared to 7.3 (95%CI; 6.3-7.9) months for trial and real-world patients. PSM resulted in 310 (30.6%) matched patients with similar survival (p=0.9). Unmatched patients had high ECOG PS or symptomatic BM.

Conclusions: Real-world patients had baseline characteristics with higher risk, and prior to adjusting for this, a poorer survival than trial patients. Patient populations in a registry with similar entry criteria as patients treated in post-approval trials have the same outcomes. In this case, the DMTR could replace post-approval studies in the medicines evaluation after marketing authorization.

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1121P Factors predicting overall survival (OS) and progression-free survival (PFS) in real-life: Classification and regression tree analysis of a 5-year (5Y) cohort follow-up study of advanced melanoma patients (pts) that have initiated pembrolizumab

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Background: Factors predicting OS and PFS in anti-PD-1-treated melanoma pts are unknown in real-life pts, where brain metastasis or ECOG performance status >1 are frequent. Likewise, the prognostic value of AJCC staging (7th and 8th editions) remains unknown in this population.

Methods: HORIZON is a multicenter ambispective cohort of advanced melanoma pts who initiated pembrolizumab (2 mg/kg/3w) during the French Early Access Program (ATU, 5/2014 to 9/2015, CCTIRS #15.640) and were followed up to 5Y. Multivariate analyses first selected candidate variables among ECOG, serum LDH, N organs with metastasis <3 or ≥3, naïve vs non-naïve, brain or liver metastasis, AJCC7 and AJCC8 scores. All variables associated with OS and PFS were classified by classification and regression tree (CART); Kaplan-Meier analyses of OS and PFS were performed on identified pt groups, with multivariate Cox regressions (significance, $p<0.05$). Data cut-off: 18/11/2019.

Results: 705 pts (161 with brain metastasis and 125 ECOG >1) were included in 41 centers. Based on CART analysis, with the AJCC7, a combination of ECOG status, serum LDH and AJCC7 score best predicted 1-, 2- and 3-Y OS, while ECOG and AJCC7 scores alone best predicted PFS. Using AJCC8, a combination of ECOG, serum LDH and AJCC8 score best fit OS, and a combination of ECOG, serum LDH, AJCC8 score, and the presence of liver metastasis best fit PFS. Brain metastatasis was not selected in any of the CART analyses. Using AJCC7, the best OS was observed in pts with ECOG ≤1 and an AJCC7 score M1A/B, and the worst in pts with ECOG >1 and high serum LDH (HR 9.2, 95%CI [6.4—13.3]). When using AJCC8, the best OS was observed in pts with ECOG ≤1, normal serum LDH and an AJCC score M1A/B and the worst in pts with ECOG >1 and an elevated serum LDH (HR 9.43, 95%CI [6.5—13.6]). Multivariate analyses, regression tree models and survival curves will be presented.

Conclusions: ECOG status was the main factor associated with OS and PFS, with an additional prognostic value provided by LDH serum levels and AJCC scores (both the 7th and 8th editions). We would like to thank to the entire RIC-Mel network team.

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1122P Real-world analysis of dabrafenib plus trametinib in patients with BRAFV600-mutated melanoma brain metastases

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Background: Despite the availability of improved treatment options in *BRAFV600* mutation-positive metastatic melanoma, limited evidence exists for the treatment of melanoma patients (pts) with brain metastases (BMs). The non-interventional study COMBI-r evaluates the treatment of *BRAFV600*-mutated melanoma with the BRAF/MEK inhibitor combination dabrafenib plus trametinib (D+T) in clinical routine. A recent analysis confirmed the effectiveness and safety of D+T. Here, we focus on real-world demographics and outcomes of melanoma pts with and without (w/o) BMs.

Methods: Between Dec 2015 and Dec 2018, 502 pts at 58 German centers were included in COMBI-r. Effectiveness and safety of D+T were assessed in pts treated for at least 1 year or who had stopped treatment. 273 pts had stage IV disease at baseline; 100 pts had BMs and 173 pts had no BMs. Effectiveness of D+T and demographics were described and integrated with slow, intermediate and fast tumor dynamics, which were based on the physician's objective assessment of clinical parameters including stage, LDH and metastatic spread.

Results: Median progression-free survival in pts with BMs was 6.1 months (CI 95% 5.2-6.9) vs 10.5 months (CI 95% 8.8-11.7) w/o BMs. The objective response rate (ORR) in pts with BMs was 31.9% while 3.3% achieved a complete response (CR). Pts w/o BMs had an ORR of 44.5% with 10.3% reaching a CR. Median duration of treatment was 6.3 months in pts with BMs and 7.0 months w/o BMs. 17% of pts w/o BMs had been assigned to slow tumor dynamics compared to 10% of pts with BMs; all other tumor dynamics subgroups were similar. Incidence rates of adverse events (AEs) were comparable with reported phase III data, although rates of common AEs, such as pyrexia, fatigue and skin-related toxicities, were lower.

Conclusions: The COMBI-r interim analysis provides evidence of the clinical benefit of D+T in pts with *BRAFV600*-mutated BMs. These real-world data are comparable to the phase II melanoma BMs trial COMBI-MB. Although AE rates were lower, the overall safety profile was consistent with previous phase III melanoma data. Nevertheless, the results illustrate the vast difference in clinical outcomes between melanoma pts with and w/o BMs underscoring the high medical need of this pt population.

Clinical trial identification: COMBI-r, non-Interventional Study.

Legal entity responsible for the study: Novartis.

Funding: Novartis.

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1123P A phase Ib study of rose bengal disodium and anti-PD-1 in metastatic cutaneous melanoma: Initial results in patients refractory to checkpoint blockade

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Background: PV-10 (10% rose bengal disodium for injection) is a small molecule autolytic immunotherapy in development for solid tumors; intralesional (IL) injection can yield immunogenic cell death and induce tumor-specific reactivity in circulating T cells. Functional T cell response may be enhanced through combination with immune checkpoint blockade (CB).

Methods: PV-10-MM-1201 (NCT02557321) is a phase 1b/2 study of IL PV-10 in combination with systemic anti-PD-1 (pembrolizumab, "pembro") for patients (pts) with advanced cutaneous melanoma; pts must have at least 1 injectable lesion and be candidates for pembro. The combination is administered q3w for 5 cycles followed by pembro alone q3w for up to 24 months. The primary endpoint is safety and tolerability, with objective response rate (ORR) and progression-free survival (PFS) as key secondary endpoints (assessed by RECIST 1.1 after 5 cycles then q12w). Immune correlative assessments are being performed on a subgroup of pts.

Results: We report initial results of an expansion cohort of melanoma pts refractory to CB, an indication with unmet clinical need. Pts (N = 13: 1 Stage IIIC, 1 IIID, 4 M1a, 2 M1b, 3 M1c, 2 M1d; median age 77 years, range 54-90) had one or more prior lines of CB (2 pts were refractory to CTLA-4, 4 to PD-1 and 7 to CTLA-4 and PD-1). Adverse events were consistent with established patterns for each drug. This initial group achieved an ORR of 31% (PRs among 4 IIIC, IIID, M1a, and M1d pts), while 2 pts (M1a and M1c) achieved SD, for a disease control rate of 46%. Four pts have completed correlative assessment: 2 of these pts exhibited increased High Mobility Group Box 1 (HMGB1), a Damage Associated Molecular Pattern (DAMP) molecule associated with activation of dendritic cells, in post-PV-10 serum; and 1 pt (M1a refractory to CTLA-4 and PD-1) also exhibited increased T cell reactivity to HLA-matched tumor 7 days after initiation of PV-10 treatment that preceded achieving a durable PR.

Conclusions: Acceptable safety and tolerability were observed, supporting ongoing enrollment. Pharmacodynamic assessments are consistent with the immune-mediated mechanism of action of PV-10 in this CB-refractory population.

Clinical trial identification: NCT02557321.

Legal entity responsible for the study: Provectus Biopharmaceuticals, Inc.

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Disclosure: E. Wachter: Leadership role, Full/Part-time employment: Provectus Biopharmaceuticals. All other authors have declared no conflicts of interest.

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1124P Phase Ib study to evaluate the safety of selinexor (SEL) in combination with pembrolizumab (PEM) in patients with advanced malignancies- the: The melanoma experience

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Background: Selinexor is a first-in-class novel, oral potent selective inhibitor of nuclear export, which inhibits the transport protein Exportin-1. Preclinical models have suggested that SEL in combination with checkpoint inhibitor (CPI) would enhance the ability to inhibit the proliferation and survival of tumor cells.

Methods: This open label, single center phase IB combination therapy study in metastatic/locally advanced cancers enrolled either treatment naïve (t/n) pts or pts who relapsed on prior therapies (r/p). The addition of SEL to multiple standard chemotherapy and CPI regimens was tested in parallel, with ARM L using PEM (200g IV q3 weeks) in combination with SEL (starting dose 60mg PO BIW). For this melanoma (MM) cohort, we used recommended phase II dose (RP2D) data obtained from the dose escalation. Primary objective was to establish the safety and tolerability of SEL/PEM. Secondary endpoints included response rate (RR) and progression free survival (PFS).

Results: 25 pts MM (13 male) have enrolled, including 6 pts with uveal MM, with a median age of 65.8 years (range 31.4-83). The majority of patients (n=17) had no prior systemic therapies for MM, but 5 pts had +/>3 lines of prior therapy. Most common SEL or PEM related AEs included nausea (68%), vomiting (52%), and anemia (48%). Three pts discontinued therapy due to AE. At a median follow up of 4.8 months (range 0.1-14.0) three pts achieved a CR (13%), 6 achieved a PR (26%) and 10 (43%) had stable disease (SD). Specifically, the overall RR in non-uveal t/n pts, 54% achieved either a CR (23%) or PR (31%). None of the uveal MM responded (5 pts SD). The median PFS for the entire cohort has not been reached and the 6-month PFS rate was 0.65 (95% CI: 0.46, 0.91). The 9-month PFS rate was 0.57 (95% CI: 0.37, 0.87). The median overall survival (OS) has not been reached, and the 6 months OS rate of 0.81 (95% CI: 0.63, 1). 22/25 pts are still alive.

Conclusions: The RP2D dose was Selinexor 60 mg po BIW and q 3 week PEM in patients with MM. Treatment with SEL/PEM is well-tolerated and shows significant clinical activity with a ORR of 54% compared to historical ORR of 30% with single agent PEM in t/n pts compared to historic single agent PEM. The combination warrants further evaluation.

Clinical trial identification: NCT02419495.

Legal entity responsible for the study: University of Texas MD Anderson Cancer Center.

Funding: Karyopharm Therapeutics, Inc.

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1125P A phase Ib study of rose bengal disodium and anti-PD-1 in metastatic cutaneous melanoma: Results in patients naïve to immune checkpoint blockade

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Background: PV-10 (10% rose bengal disodium for injection) is a small molecule autolytic immunotherapy in development for solid tumors; intralesional (IL) injection can yield immunogenic cell death and induce tumor-specific reactivity in circulating T cells. Functional T cell response may be enhanced through combination with immune checkpoint blockade (CB).

Methods: PV-10-MM-1201 (NCT02557321) is a phase 1b/2 study of IL PV-10 in combination with systemic anti-PD-1 (pembrolizumab, "pembro") for patients (pts) with advanced cutaneous melanoma. Eligibility for the main cohort of phase 1b required pts to have at least 1 injectable lesion, be CB-naïve, and be candidates for pembro. The combination was administered q3w for 5 cycles followed by pembro alone q3w for up to 24 months. The primary endpoint was safety and tolerability, with objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) as key secondary endpoints (assessed by RECIST 1.1 after 5 cycles then q12w).

Results: Full accrual of the main cohort was reached in April 2018 and final response assessments were competed in April 2020, with 21 CB-naïve pts (2 IIIC/IIID, 8 M1a, 7 M1b, 4 M1c; median age 69 years, range 28-82) receiving at least 1 dose of PV-10 and pembro (2 enrolled pts with prior CB treatment are not included here). Treatment-Emergent Adverse Events were consistent with established patterns for each drug, principally Grade 1-2 injection site reactions attributed to PV-10 and Grade 1-3 immune-mediated reactions attributed to pembro, with no significant overlap or unexpected toxicities. Among this predominantly Stage IV population, an ORR of 67% was achieved, with 10% CR (1 pt each with M1a and M1b disease) and 57% PR (including all M1c pts). Median PFS was estimated at 11.7 months. Median OS was not reached (landmark overall survival was 92% and 62% at 1 and 2 years, respectively); disease-specific survival was 100% and 65% at 1 and 2 years, respectively.

Conclusions: The primary endpoint for phase 1b was met, with acceptable safety and tolerability and no unexpected safety issues identified. Two phase 1b expansion cohorts (24 pts each) are enrolling pts refractory to prior CB and pts with in-transit or satellite disease.

Clinical trial identification: NCT02557321.

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1126P Prediction of clinical outcome by soluble immune checkpoints and T cell subsets in patients treated with immune checkpoint blockers for metastasized melanoma

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Background: Resistance to immune checkpoint inhibitors (ICIs) is still far from understood. Identifying clinical useful biomarkers might improve drug selection and patients' therapy.

Methods: We analyzed the soluble immune checkpoints sPD1, sPDL1, sLAG3 and sTIM3 using ELISA in paired serum samples of 90 ICI treated melanoma patients before and 6 weeks after start of anti-PD1 +/- ipilimumab. FACS analysis on circulating T cells was performed in 48 of these patients. In a partially overlapping cohort of 76 patients, pre-treatment biopsies from melanoma metastases were stained for TIM3 and LAG3 by immunohistochemistry. Results were correlated with clinical parameters using univariate and multivariate regression analyses.

Results: Resistance to anti-PD1 treatment (n=48) was associated with high levels of sLAG3 (DCR: p=0.009; PFS: p=0.018; ROC cut off > 148 pg/mL) in pre-treatment serum samples but not sPD1, sPDL1 or sTIM3. In contrast, resistance to ipilimumab plus nivolumab (n=42) was associated with high sPD1 levels (DCR: p=0.019, PFS: p=0.046; ROC cut off > 167 pg/mL) but not sPDL1, sLAG3 or sTIM3. Both treatment regimens shared a profound increase of sPD1 serum levels with treatment (p=0.000). FACS analysis of the T cell subsets revealed reduced frequencies of CD3+CD8+PD1+ T

cells (p=0.036) in PD1-resistant patients whereas, increased frequencies of CD3+CD4+LAG3+ T cells characterized patients resistant to ipilimumab plus nivolumab (p=0.034). Unlike anti-PD1 monotherapy, combination blockade significantly increased proliferating T cells (CD3+CD8+Ki67+ T cells; p=0.000) and eosinophils (p=0.02) in the peripheral blood. Interestingly, the concentration of sPD1 inversely correlated with lymphocyte counts and the frequency of PD1+ T cells, and positively correlated with the frequency of TIM3+ and LAG3+ T cells. In melanoma metastases, an increased infiltration with TIM3+ or LAG3+ T cells in the tumor microenvironment correlated with a shorter PFS to anti-PD1 (TIM3: p=0.024, LAG3: p=0.027).

Conclusions: Different soluble immune checkpoints characterized checkpoint inhibitor resistant melanoma. Measuring these serum markers is easy and has the potential to be used in clinical routine.

Legal entity responsible for the study: The authors (JC Hassel).

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1127P Correlation of BRAF mutation status in circulating tumour DNA (ctDNA) with tumour biopsy and clinical outcomes in COLUMBUS

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Background: ctDNA testing offers a less invasive alternative to biopsy for identifying *BRAF*-positive patients (pts) with melanoma who are candidates for targeted therapy, and may have prognostic value. We assessed the concordance between ctDNA and tumour tissue *BRAF* mutation status, and clinical relevance of ctDNA *BRAF* mutation status, using data from COLUMBUS.

Methods: In COLUMBUS part 1, 577 pts with advanced/metastatic *BRAF* V600-mutant melanoma, untreated or progressed after first-line immunotherapy, were randomized 1:1:1 to encorafenib 450 mg QD + binimetinib 45 mg BID, encorafenib 300 mg QD or vemurafenib 960 mg BID. A total of 613 plasma samples were collected during screening. *BRAF* V600E/K in ctDNA were assessed using BEAMing technology, and concordance of *BRAF* status between baseline (BL) ctDNA and tissue was assessed. Associations of ctDNA *BRAF* V600E/K mutation status (yes/no) with BL markers of poor prognosis and centrally confirmed overall response rates (ORRs) were analysed. Data are as-is and the trial is ongoing.

Results: In total, 502 pts had results for both ctDNA and tissue *BRAF* V600E/K assessments. Of these pts, 317 (63%) had *BRAF* V600E/K detected by ctDNA, and 420 (84%) had *BRAF* V600E/K by tissue. Overall agreement (positive agreement; negative agreement) of ctDNA versus tumour tissue was 78% (75%; 96%) for *BRAF* V600E/K, 81% (75%; 99%) for *BRAF* V600E and 97% (70%; 99%) for *BRAF* V600K. *BRAF* V600E/K detectable by ctDNA were associated with higher lactate dehydrogenase levels, greater number of organs with disease, and greater tumour burden at BL (unadjusted Wilcoxon 2-sample p<0.0001 for each). Within each treatment arm, there were no notable ORR differences between ctDNA *BRAF* mutation status (95% CIs overlapped; Table).

Table: 1127P ctDNA BRAF mutation status and ORR by treatment arm

ctDNA *BRAF* V600E/K mutation	Centrally confirmed ORR, % (95% CI)		
	Encorafenib 450 mg QD + binimetinib 45 mg BID	Encorafenib 300 mg QD	Vemurafenib 960 mg BID
Yes	69.3 (57.6–79.5)	57.5 (45.9–68.5)	42.3 (31.2–54.0)
No	53.3 (34.3–71.7)	60.0 (38.7–78.9)	40.7 (22.4–61.2)

Conclusions: These findings confirm the reliability of ctDNA for detecting *BRAF* mutations; ctDNA may serve as an alternative test for *BRAF* V600E/K mutations. ctDNA *BRAF* mutations correlated with BL markers of poor prognosis but not with ORR.

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1128P Germline variation in PDCD1 is associated with survival in metastatic melanoma after anti-PD-1 monotherapy

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Background: Interaction of the programmed cell death-1 (PD-1) receptor with its ligands leads to downregulation of the T cell effector function and impairs antitumor immunity. Immune checkpoint inhibitors (ICIs) targeting PD-1 have proven efficacy in patients with several malignancies. Single nucleotide polymorphisms (SNPs) in genes related to the PD-1 axis likely affect T cell response upon anti-PD treatment. In fact, specific SNPs in the *PDCD1* gene downregulate expression of PD-1 by T cells and are associated with decreased susceptibility to cancer. In this study, we investigated whether SNPs in genes related to the PD-1 axis are predictive of survival in metastatic melanoma patients treated with anti-PD-1 monotherapy.

Methods: Consecutive patients with metastatic melanoma who were treated either with nivolumab or pembrolizumab were included. Prospectively collected samples were genotyped for SNPs in *HLAA* (rs60131261), *GZMB* (rs8192917), *IL-10* (rs3024493), *IL2RA* (rs2104286), *IL-2RB* (rs3218253), *IFNG* (rs2430561; rs2069705; rs2069718), *PDCD1* (rs2227981), *PTPN11* (rs2301756), and *ZAP70* (rs13420683). Associations between SNPs and overall survival (OS) or progression free survival (PFS) were tested using Cox regression analysis. Associations with $p \leq 0.10$ were tested multivariably and internally validated by bootstrapping.

Results: In total, 119 patients were included. The median follow-up was 2.6 years. Variation of *PDCD1* (rs2227981) and *GZMB* (rs8192917) showed a trend towards OS (HR 2.03; 95%CI: 0.10-4.12; p 0.051 and HR 1.81; 95%CI: 0.95-3.36; p 0.060, respectively) and PFS (*GZMB:* HR 1.63; 95%CI: 1.00-2.67; p 0.051). After correction for prognostic factors (i.e. age, ECOG performance status and LDH), only variation of *PDCD1* remained significantly associated with poorer OS (HR 2.37; 95%CI: 1.11-5.04; p 0.026), which was internally validated (Bias-corrected 95%CI: 1.04-6.25).

Conclusions: Patients with metastatic melanoma who have germline variation of *PDCD1* have a significant poorer overall survival after anti-PD-1 monotherapy. These findings suggest that germline variations in immune-related genes are relevant for response and resistance to ICIs, which could be further explored in genome wide association studies.

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1129P Copy number alterations in 9q are linked to prognosis in cutaneous melanoma

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Background: Cytogenetic studies reveal a large amount of chromosomal aberrations in 95% of melanoma cases. The goal of this study was to evaluate the prognostic significance of the most common chromosomal copy number alterations in melanomas with and without metastasis.

Methods: We investigated the association between copy number alterations, both gains and losses, and clinical outcome in 400 melanoma patients from the Cancer Genome Atlas (TCGA) cohort (89 had stage I, 117 stage II, 144 stage III and 20 stage IV) after a median 4-year follow-up. The data analysis was done using clinical and genetic TCGA datasets available at cbioportal.org. Copy number alterations were identified using data on chromosome-arm-level across the entire genome in tumor samples (primary 62%, regional 32%, and distant 16%). Survival distributions were estimated according to the method of Kaplan and Meier and the significance was tested with the log-rank statistic. Cox proportional hazards regression model were used to analyze the relationship between the frequency of copy number changes, tumor stage, and patient age.

Results: Chromosomal copy number losses were slightly more common than gains (2309 versus 1772); 13.47% and 10.52% of total copies analyzed respectively. Median aneuploidy score was 11 (range, 0-35 aberrations/tumor). The most frequent losses include deletions at 9p (60.35%), 10q (53.5%), 6q and 9q (47%). Frequent gains may occur at 7 (47%), 8q (42%), 1q (40.8%) and 6p (35.3%). The status of chromosome 9q was the only chromosomal alteration related to overall survival (OS) significantly in univariate analysis. Patients with 9p gain had a lower OS rate (43.8) than not call (78.9) or loss (94.9) months; p-0.018. A multivariate analysis identified young age <65 years (HR-0.5 p-0.0001; initial stages of disease: Stage I (HR-0.31 p-0.03) or Stage II (HR-0.38 p-0.016); and status of chromosome 9q (p-0.010): 9q loss (HR-0.42 p-0.005) as being independently associated with long survival.

Conclusions: Here, we provided functional evidence that copy number alterations of chromosome 9q are thought to play integral roles in melanoma prognosis. A targeted list of genes located in 9q could represent future prognostic molecular biomarkers.

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1130P BRAF and MEK inhibition in CDKN2A germline carriers and BRAF mutant melanoma

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Background: Inherited pathogenic variants (PV) in the *CDKN2A* tumour suppressor gene are among the strongest known risk factors for cutaneous melanoma. *CDKN2A* encodes for the cell cycle inhibitors $p16^{ink4}$ and p14ARF, and dysregulation of the p16/RB1 pathway is a well-known mechanism of resistance to MAPK-directed targeted therapy due to the interplay between the two pathways. For this reason, we wondered whether patients with germline *CDKN2A* PVs may achieve suboptimal results with BRAF and MEK inhibitors.

Methods: We identified twenty *CDKN2A* PVs carriers who received first-line treatment with BRAF and MEK inhibitors for BRAF-mutant advanced melanoma by reviewing medical records of carriers enrolled in follow-up studies for familial melanoma. By a binomial test, we evaluated if there was a statistically significant difference in the response rate observed in the carriers compared with an expected rate calculated from phase III clinical trials and "real-world" studies.

Results: The baseline prognostic features of the 20 identified patients were poorer than those reported in phase III clinical trials, with 12 patients (60%) having stage M1c disease and 5 patients (25%) brain metastases at baseline. Seventeen patients (85%) achieved a partial response; no complete responses were observed. The overall response rate was numerically higher than that expected from phase III trials (66%), although not statistically significant (p-value=0.097; 95% CI: 0.62-0.97); the difference was statistically significant (p-value=0.012; 95% CI: 0.62-0.97) when the comparison was performed with real-world studies.

Conclusions: The clinical activity of BRAF and MEK inhibitors in patients with BRAF-mutant advanced melanoma and germline *CDKN2A* PVs was not inferior to that observed in clinical trials and real-world studies, which we believe is helpful information for clinicians who manage patients with melanoma.

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1131P C-reactive protein as biomarker for immune-related adverse events in melanoma patients treated with immune checkpoint inhibitors in the adjuvant setting

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Background: Immune checkpoint inhibitors (ICIs) are a standard of care adjuvant treatment option for melanoma patients following the resection of lymph node metastases. ICIs are associated with potentially severe immune-related adverse events (irAEs) and early diagnosis of irAE is of importance. We evaluated the utility of C-reactive protein (CRP) as a biomarker for the early diagnosis of irAEs in melanoma pts treated with ICI in the adjuvant setting, and its potential correlation with relapse-free survival.

Methods: Prospectively collected data from 72 melanoma patients treated with ICIs in the adjuvant setting in a prospective phase II trial (NCT02941744, Schwarze JK et al. JCO. 2019;37(15_suppl):9585) and an observational trial were pooled. CRP-values enveloping 9 defined categories of irAEs were analysed.

Results: A total of 191 irAEs (grade 1 or 2, n=182; grade 3 or 4, n=9) occurred in 64 patients (skin toxicity [n=70], fatigue [n=50], thyroiditis [n=12], musculoskeletal toxicity [n=11], sicca syndrome [n=10], pneumonitis [n=6], colitis [n=4], hepatitis [n=3] and hypophysitis [n=2]). An additional 23 irAEs did not match any of these most frequent categories. In ir-pneumonitis and ir-hypophysitis the median serum CRP-levels exceeded the ULN (5mg/L) with a mean rise of 21.0 mg/L and 9.7 mg/L respectively. Declining CRP-levels were correlated with recovery of an irAE and increases in CRP-level indicated relapse of the irAE. With a median follow-up of 26.5 months 28 patients (39%) were diagnosed with a melanoma relapse. Patients who experienced no irAE were at the highest risk for relapse. Patients diagnosed with an irAE that was associated with an elevated CRP (>2xULN) were at higher risk for relapse as compared to those diagnosed with an irAE and CRP <2xULN (Log Rank, descriptive *p*-value of .054).

Conclusions: CRP has potential as a biomarker for the early detection of selected irAEs. Monitoring of CRP-levels during adjuvant ICI treatment could help safeguarding adjuvant ICI therapy in daily clinical practice. The observed correlation between irAEs associated with an elevated CRP and risk for recurrence deserves further investigation.

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1132P DNA damage repair mutation burden (DDRMB) was significantly associated with TMB and predicted prognosis of immunotherapy in melanoma

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Background: Tumor mutation burden (TMB) was emerging biomarker and was associated with prognosis of immunotherapy. Mutations in DNA damage repair (DDR) pathway hampers DNA damage repair and would lead to accumulation of mutations, which might increase TMB. Although there were sporadic reports about association between mutation in certain DDR genes (such as TP53, BRCA1/2, BER) and tumor prognosis, the association between DNA damage repair mutation burden (DDRMB), and TMB and prognosis of immunotherapy was not well evaluated yet.

Methods: We retrospectively analyzed the whole exome sequencing (WES) results of 110 and 64 patients from 2 published prospective studies in melanoma and their prognosis of immunotherapy. 201 genes were defined as DDR genes. Correlation between DDRMB and TMB was analyzed. Difference in prognosis was conveyed by Kaplan-Meier analysis. Difference of TMB between groups were conveyed by T test.

Results: Strong correlation between DDRMB and TMB was revealed (R^2=0.8798). TMB in patients with DDR mutations was significantly higher than others (P<0.001). Patients were divided into 4 subgroups with $\geq$ 3, 2, 1 and 0 DDR mutations. Pairwise comparison among each group indicated that groups with more DDR mutations contained significantly higher TMB than groups with less mutations (P<0.001). The overall survival (OS) in patients with DDR mutation was significantly higher than patients without DDR mutation (P=0.05). Besides, subgroups with $\geq$ 3 DDR mutations showed numerically longer OS than patient with less mutations.

Conclusions: DDR mutation burden was highly correlated with TMB. Melanoma patients with higher DDRMB bears higher TMB, and showed worse OS in immunotherapy. DDRMB might be a potential biomarker for immunotherapy in melanoma. Larger trials are needed for further validation.

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1133P Skin photoaging around the site of occurrence of primary melanoma as a clinical predictive biomarker of response to PD-1 inhibitors

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Background: Cutaneous melanomas have a high tumor mutational burden (TMB) because of mutations induced by ultraviolet radiations (UVR). TMB is a predictive biomarker of response to PD-1 inhibitors but it is unfortunately not yet routinely available. Considering photoaging as a result of repeated and cumulative exposure to UVR, we hypothesized that signs of photoaging around primary melanoma could predict response to PD-1 inhibitors.

Methods: We conducted a retrospective bicentric study including 34 patients with stage IV melanoma treated with first-line immunotherapy. Five independent dermatologists assessed the grade of photoaging for each patient using two clinical scales, one descriptive and the second photo-analogic (McKenzie Photographic Scale), in a blinded, photographic assessment. The reliability of the clinical scales was statistically assessed by intraclass correlation coefficients (ICC). Outcomes were progression-free survival (PFS), overall survival (OS), and objective response rate (ORR).

Results: The clinical scales, graded from 0 to 3, were reproducible, with an ICC of 0.68 for the descriptive scale and 0.72 for the photo-analogic scale. PFS was significantly higher in case of severe photoaging with both the descriptive scale and the photo-analogic scale (HR=0.32, p<10-3, and HR 0.41, <10-3, respectively). Similarly, OS was higher when photoaging was assessed severe. Three-month ORR was better in cases of severe photoaging than in cases of mild/no photoaging, both with the descriptive and photo-analogic scales (77% vs. 24% and 61% vs. 25% respectively).

Conclusions: Our study suggests that reliable determination of photoaging around a melanoma or its scar can be used as a predictive clinical biomarker of response to PD-1 inhibitors, higher grades being associated with better response rate and progression-free survival.

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1134P BRAF codon 600 mutations in patients diagnosed with melanoma in the UK; An audit to assess variation in mutation frequency & methods between clinical testing centres

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Background: The published frequency of the BRAF p.V600 mutations in patients with melanoma is approximately 40% and is dependent on age and melanoma subtype. BRAF status is a key predictive factor for response to targeted therapy and immunotherapy and there is increasing evidence that it is also prognostic. Mutation testing is a standard of care for patients with resected Stage 3 and for Stage 4 disease, to inform treatment choice. There are currently a variety of validated and approved methods for BRAF testing. The primary aim of this study was to identify all clinical laboratories in the UK performing BRAF testing for melanoma and examine the assays used, positivity rates and turnaround time.

Methods: This was a retrospective audit of laboratories performing BRAF gene mutational analysis in melanoma samples in the UK. 14 out of the 18 identified laboratories participated. Methodologies used and anonymised results for samples tested Jan-Dec 2019 were collected.

Results: 4050 results were analysed. The median BRAF positivity rate amongst all laboratories was 34% (range 23-41%). The median turnaround time for reporting results was 7 calendar days. 6 laboratories used only one method of testing and 8 laboratories used more than one. The types of tests used varied between the testing centres. All laboratories are able to detect clinically important BRAF p.V600E and p.V600K mutations. Men (p= 0.0354) and younger patients (p <0.001) had higher rates of BRAF mutation. the range of median age per laboratory was 65-72.

Conclusions: The median reported BRAF positivity rates in the UK is lower than published and there is a wide range. The reasons for the difference in the positivity rates are likely multiple but could potentially have an impact on treatment options offered to patients. Further research is required to identify the reasons for these differences. This will include collaboration with the UK National External Quality Assessment Scheme to optimise the methodologies used across centres, aiming for more consistent results across the board.

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1135P Plasma proteomics in patients with metastatic cutaneous melanoma treated with targeted therapy

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Background: Targeted therapy have significantly improved the outcome in *BRAF*V600-mutated metastatic cutaneous melanoma (CM). These therapies induce rapid therapy response in *BRAF*V600E/K disease and can be used alone or in combination (i.e. MEK- and/or BRAF-inhibitors). Although the 5-year overall survival and progression free survival (PFS) are comparable to the results from anti-PD-1 therapy for metastatic CM, resistance often occurs within 6-12 months. Clinically useful treatment predictive biomarkers are lacking. Previously, we have demonstrated that unbiased mass-spectrometry-based in-depth proteomics with high resolution isolelectric focusing, liquid chromatography, mass spectrometry (HiRIEF LC-MS/MS) is able to quantify over 1,000 proteins, including circulating and tissue-derived proteins. Recently, we have reported that HiRIEF LC-MS/MS, with adjuvant targeted proteomic analyses, provided us with a unique and previously unexplored view into the dynamic changes of the proteins present in plasma of metastatic melanoma patients receiving immune checkpoint blockade (ICB), and the ability to detect peptide-coding variants in plasma. Moreover, we showed that the major plasma proteome changes in patients treated with ICB were not detectable in patients treated with targeted therapy, which we analysed for comparison.

Methods: Serial plasma samples from 24 patients with metastatic CM patients receiving targeted therapy were analyzed with a mass-spectrometry proteomics method (HiRIEF LC-MS/MS) and proximity extension assays (PEA). The aim was to investigate systemic biological processes and we estimate the predictive relation between protein plasma levels and PFS as well as tracing numerous proteins back to metastatic CM tissue using TCGA transcriptomics data.

Results: Unbiased MS proteome analysis indicated plasma levels alterations related to treatment in 84 out of 1,160 proteins. In total, 38 proteins were associated with PFS. EPHA1, CPB1, and ICAM3 detected in the analysis of responders were associated with longer PFS. CTSB and SNCA.were associated with shorter PFS. SFTPA and ADGRL4 correlated with PFS.

Conclusions: Several protein signatures linked to melanoma or biological processes during targeted therapy were detected.

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1136P Feasibility of linking the UK 100,000 genomes project and real-world evidence databases for a melanoma patient population

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Background: Linking genomic and real-world evidence (RWE) datasets has the potential to generate insights to inform clinical research or practice, including identifying biomarkers associated with treatment response. This study explored the feasibility of linking genomic and RWE data for melanoma patients within the UK 100,000 Genomes Project.

Methods: Anonymised whole-genome sequencing (WGS) data for patients with melanoma were linked, using unique identifiers, to corresponding records in RWE datasets maintained by the UK National Health Service and Public Health England (PHE). Examined characteristics included demographics, melanoma type and stage, and risk factors. The 20 most commonly mutated genes were determined for the categories of actionable genes, other cancer-related genes, and non-actionable and non-cancer-related genes. Treatment-related outcomes included time on treatment (to next line or death), and overall survival from the start of first line therapy.

Results: A total of 337 melanoma patients with WGS data were identified and linked to RWE records. While demographic data (e.g. age, gender, and race) were widely available, melanoma risk factors (e.g. UV exposure) and disease characteristics (e.g. tumour stage) were often missing. Treatment outcomes were difficult to estimate due to availability and discordant cut-off dates across WGS, treatment, and death datasets (April 2020, December 2017, and November 2019, respectively). Almost all patients (97%) had at least one mutated non-actionable but cancer-related gene. The most commonly mutated actionable genes were *BRAF* (42% of patients) — particularly to BRAF-V600E (30%) — and *NRAS* (28%). Among other cancer-related genes, *LRP1B* and *FAT4* were the most commonly mutated (40% and 37%).

Conclusions: Substantial and valuable WGS data are available for patients with melanoma within the 100,000 Genomes Project, and genomic characteristics appear consistent with other cohorts. However, RWE linkage is challenging, particularly as PHE clinical data are less current than the corresponding WGS data. Current efforts to secure further sources and increase data release frequency will improve feasibility.

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1137P Incidence and time course of adverse events (AEs) with atezolizumab (A) in combination with vemurafenib (V) and cobimetinib (C) in the phase III IMspire150 study

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Background: The phase III IMspire150 study (NCT02908672) demonstrated improved progression-free survival with first-line A vs placebo (P) combined with V+C in patients (pts) with $BRAF^{V600}$ mutation—positive advanced melanoma. Safety profiles of A and V+C partially overlap. Here we report incidence, time course, and outcomes of select AEs of special interest (AESIs) in IMspire150.

Methods: 514 pts were randomized 1:1 to A+V+C or P+V+C. Pts received V+C from cycle 1; A or P was added from cycle 2 onward. Incidence (overall and by cycle), time to onset/resolution, and recurrence of select AESIs were evaluated in the safety population (A+V+C, n=230; P+V+C, n=281). Rash and hepatitis were analyzed as overall combined medical concepts.

Results: Median follow-up was 18.9 mo. AESI rates were numerically higher with A+V+C vs P+V+C (rash, 81% vs 77%; elevated creatine phosphokinase [eCPK], 53% vs 47%; pyrexia, 49% vs 35%; and hepatitis [clinical diagnosis and asymptomatic lab abnormalities], 53% vs 38%), excepting diarrhea (50% vs 56%). Incidences of diarrhea, rash, and eCPK were highest in cycle 1 and decreased thereafter. Incidences of pyrexia and hepatitis peaked in cycle 2 after addition of A in the A+V+C arm then similarly declined. Median time to onset was similar with A+V+C vs P+V+C for diarrhea (0.4 vs 0.4 mo) and rash (0.5 vs 0.4 mo), but was numerically longer with A+V+C for eCPK (1.4 vs 0.7 mo), pyrexia (1.2 vs 0.7 mo), and hepatitis (1.6 vs 1.2 mo). Median time to resolution was similar between arms (diarrhea, 0.3 vs 0.2 mo; rash, 0.8 vs 0.8 mo; eCPK, 0.5 vs 0.5 mo; pyrexia, 0.1 vs 0.1 mo; hepatitis, 0.7 vs 0.7 mo). In pts who had first occurrence of an AESI with A+V+C vs P+V+C, incidences of recurrent AESIs were diarrhea (58/115 vs 64/157), rash (65/187 vs 62/215), eCPK (62/121 vs 61/133), pyrexia (53/112 vs 29/98), and hepatitis (38/122 vs 25/107). Recurrent AESIs were generally grade 1/2 with median times to recurrence of 0.8-1.5 mo.

Conclusions: These data indicate that key AESIs with A+V+C occur early during treatment; are manageable, with resolution times similar to those with V+C; and have low to moderate risk of recurrence. Recurrent AESIs are generally mild to moderate in severity with no evidence of cumulative effect.

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1138P Delayed immune-related adverse events (irAEs) on anti-PD1-based therapy

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Background: IrAEs typically occur within 4 months of starting anti-PD1-based therapy (anti-PD1 +/- anti-CTLA4), but there are isolated reports of delayed irAEs (onset >12

months after commencement). This study describes the incidence, nature and management of delayed irAE in melanoma patients (pts).

Methods: Pts from 20 centres with delayed irAEs were studied. The incidence of delayed irAEs was estimated as a proportion of melanoma pts treated with anti-PD1-based therapy and surviving >1yr. irAE onset, clinical features, management and outcomes were examined.

Results: 122 pts developed a total of 144 delayed irAEs (23 after initial combination anti-PD-1 with anti-CTLA-4); with an estimated incidence of 5.7% (95% CI 4.3-7.3, 57/999 pts at sites with complete data). The median duration of therapy was 17.7 months (range 0.7-56.0), and median onset of delayed irAE was 16.3 months (range 12.0-53.2). 74% (90 pts) were on anti-PD1 at irAE onset, 12% (15 pts) were <3 months from last dose, 14% (17 pts) were >3 months from last dose of anti-PD1. The most common delayed irAEs were colitis, rash and pneumonitis (Table); 16% (19 pts) had multiple delayed irAEs, 39% (56 irAEs) were ≥G3. Steroids were required in 66% (81 pts), as well as an additional immunosuppressive agent in 23% (28 pts). There were 2 irAE-related deaths; encephalitis with onset during anti-PD1 and a multiple organ-irAE (colon, liver, kidney, lung and haem irAE) with onset 11.4 months after ceasing anti-PD1. Early irAEs (<12 months) had also occurred in 60% (73 pts), affecting a different organ to delayed irAEs in 86% (63 pts).

Conclusions: Delayed irAEs occur in a small but relevant subset of pts, are often different to previous irAE, high grade, difficult to manage and can lead to death. Delayed irAEs mostly occur in pts still receiving anti-PD1, such that the risks of irAE need to be weighed against the benefits of continuing treatment in responding pts beyond 1 year, however pts who stopped treatment remained at risk for developing delayed irAE.

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1139P Long-term safety profile of pembrolizumab monotherapy and relationship with clinical outcome: A pooled analysis of patients with advanced melanoma

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Background: Long-term safety of pembrolizumab in metastatic melanoma was analyzed using data from phase 1—3 studies: KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006.

Methods: Safety was assessed in randomized patients who received ≥1 pembrolizumab dose. Lead-time bias was addressed via landmark analyses with patients who were progression-free before day 147.

Results: Adverse events (AEs) were analyzed for 1567 patients. Median follow-up was 42.4 months (range, 24.6-47.8), which represents the largest analysis of the safety of pembrolizumab in advanced melanoma to date. Most treatment-related AEs (TRAEs) were mild/moderate; grade 3/4 TRAEs occurred in 17.7% of patients. Two deaths were considered pembrolizumab-related. Any-grade and grade 3/4 immune-mediated AEs (imAEs) occurred in 23.0% and 6.9% of patients, respectively; imAEs occurring in ≥3.0% of patients were hypothyroidism (9.1%), pneumonitis (3.3%), and hyperthyroidism (3.0%); median time to onset/resolution was 15.9/8.6, 36.0/8.1, and 7.3/6.1 weeks. Most imAEs occurred within 16 weeks of treatment initiation. In the week-21 landmark analysis (n = 291 still on study), patients who did (n = 79) versus did not (n = 384) develop imAEs had similar objective response rates (ORRs) (64.6% vs 63.0%); median time to response (TTR) was 5.6 months for both; median duration of response (DOR) was 20.0 versus 25.3 months; median progression-free survival (PFS) was 17.0 versus 17.7 months; median overall survival (OS) was not reached (NR) versus 43 months ($P = 0.1104$). Patients who did (n = 17) versus did not (n = 62) receive systemic corticosteroids at week 21 had similar ORRs (70.6% vs 62.9%) and median TTR (6.4 vs 5.6 months) but numerically shorter median PFS (9.9 vs 17.0 months); median DOR was 14.2 months versus NR; median OS was NR for both.

Conclusions: These results further support pembrolizumab use in advanced melanoma, with no new toxicity signals after lengthy follow-up of a large patient population. In landmark analyses, pembrolizumab efficacy was similar regardless of imAE occurrence or systemic corticosteroid use.

Clinical trial identification: KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006: NCT01295827, NCT01704287, and NCT01866319, respectively.

Table: 1138P

Delayed irAE	Total patients	G1/G2	G3/G4	G5	N *(%)* requiring systemic corticosteroids	N *(%)* requiring additional immunosuppression
TOTAL n° pts with 144 irAE	122	74	46	2	81 *(66%)*	28 *(23%)*
Colitis	31 *(22%)*	13	18	0	29 *(94%)*	13 *(42%)*
Rash	26 *(18%)*	22	4	0	7 *(27%)*	1 *(4%)*
Pneumonitis	18 *(13%)*	16	2	0	17 *(94%)*	0 *(0%)*
Rheumatological	14 *(10%)*	11	3	0	9 *(64%)*	7 *(50%)*
Hepatitis	12 *(8%)*	2	10	0	10 *(83%)*	2 *(17%)*
Neurological	10 *(7%)*	3	6	1	8 *(80%)*	3 *(30%)*
Hypophysitis	7 *(5%)*	5	2	0	0 *(0%)*	0 *(0%)*
Renal	7 *(5%)*	1	6	0	7 *(100%)*	3 *(43%)*
Other	19 *(13%)*	15	4	0	5 *(26%)*	1 *(5%)*

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1140P A digital companion for patients with BRAF-mutant advanced melanoma treated with targeted therapies: TAVIE skin app

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Background: Patients with advanced melanoma are facing questions regarding their disease, their treatment, or potential signs and symptoms that are common, though predictable. Strategies to control symptoms include targeting patient education and unhealthy behaviors. In the context of an increasingly digital healthcare system, it is worth considering the role of mobile health applications (mHealth) as patient empowerment tools for routine care, patient education and treatment management. To support patients in their daily-life, a digital solution, called *TAVIE Skin*, was developed; dedicated to all BRAF-mutant unresectable or metastatic melanoma patients who are treated with targeted therapies.

Methods: The intended goal of the *TAVIE Skin* app is (i) to deliver the necessary information and education support to the patient in regards with their disease and medications, through virtual nurse coaching, (ii) to keep track of medications to improve adherence, (iii) to assist patients in identifying side effects using the virtual nurse coaching and side effects library, and (iv) to engage them towards sustainable healthy behaviors thanks to lifestyle interventions, health trackers and real time coaching. In addition, an optional patient survey is incorporated into the *TAVIE Skin* app to assess patient reported outcomes, after an e-consent is signed via the app. Ethics approval will be obtained before data collection as per local regulations.

Results: The application will be available in 5 European countries in 2020, and in other countries in 2021. The survey will include 400 patients and will allow for describing the users' profile of *TAVIE Skin* app, for assessing HRQoL, including physical, emotional, social, and functional well-being, treatment adherence, as well as work productivity and activity impairment upon targeted therapy. The patients' satisfaction toward their melanoma treatment, and toward the application will be also assessed.

Conclusions: To the best of our knowledge, *TAVIE Skin* is the first mHealth application dedicated to patients with BRAF-mutant advanced melanoma. At this year's ESMO Congress, a description of the app, the survey and their objectives will be presented.

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1141P EXCITE: An analysis of the metastatic melanoma patient experience in the advent of novel therapies using health-related social media

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Background: Novel immunotherapy (IO) and targeted therapies (TT) for metastatic melanoma (MM) have improved survival. However, limited evidence exists on patient-reported experiences of these therapies. This study aimed to understand the symptom experience of MM patients receiving IO or TT, using health-related social media.

Methods: Posts by MM patients and caregivers (users) were retrieved from publicly available melanoma-specific forums (2014-2019). Data were deidentified to protect patient privacy. The study population included users mentioning an IO or TT of interest. Machine learning was used to identify posts containing a treatment experience. Symptom mentions were captured using natural language processing. Qualitative review was conducted on a random sample of posts to uncover symptom impacts.

Results: The study included 1,037 users: 499 ipilimumab/nivolumab (IpiNivo), 451 pembrolizumab (Pembro), 443 nivolumab (Nivo), 215 dabrafenib/trametinib (DabTram), 20 encorafenib/binimetinib (EncoBini) users. Overall, fatigue was the most frequently mentioned symptom (36% of users), followed by pain (31%) and rash (20%). Fatigue was most common among Nivo (43%), IpiNivo (33%), and DabTram users (21%). Pain was most common among Pembro (32%) and EncoBini users (30%). Qualitative review included posts from 34 DabTram, 34 IpiNivo, 28 Pembro, 27 Nivo, and 18 EncoBini users. Symptom impacts were mostly physical (e.g. mobility issues, difficulty exercising and inability to drive), then psychological (e.g. anxiety, depression and feeling frustrated). Impacts on sleep and social life were reported to a lesser extent. Physical impacts were most common among DabTram (18%) and Pembro users (14%), and psychological impacts among IpiNivo (12%) and Pembro users (7%).

Conclusions: Health-related social media provide unique insights on patient experiences of novel treatments without potential reporting bias by medical teams. High frequency of symptoms such as pain and fatigue across treatment groups suggest their importance and impact on patients' lives. Future studies are needed to validate findings outside of the online community population and further investigate symptom impacts, for example patient surveys.

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1142P Treatment of metastatic uveal melanoma (mUM) through genomic profiling

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Background: There is no standard treatment for mUM. A high-throughput genomic and transcriptomic program was initiated to uncover potential targets and assign molecularly guided treatment to this "hard-to-treat" tumor.

Methods: From March 2016 to November 2019 mUM patients were included in the prospective Treat20Plus study and tumor was analyzed via a comprehensive molecular tumor analysis program. A molecular tumor board interpreted the data and issued treatment recommendations.

Results: Forty-four patients were included: 25F/19M, age: 61(24-80), ECOG: 0 (0-2), time to metastasis 3.7 years (0-36), metastatic sites: 5 (1-8), abnormal LDH: 68%, pretreated patients: 63%. Tumor cell content was too low in 6. Time from biopsy to analysis: 59 days (28-144). Mutation burden: 32 (15-459). The genetic alterations affected GNAQ (15), GNA11 (23), BAP1 (19), SF3B1 (14), EIF1AX (1), BAP1 and SF3B1 (1), PTEN (5) and NF1 (1). In addition, we found MYC gain (32), up-regulation of MET (27), BCL2 (32) and MDM2 (11). Thirty-nine patients had a treatment recommendation and 25 (64%) of them received a targeted therapy accordingly, based on off-label use of trametinib (14), selumetinib (2), crizotinib (7), cabozantinib (4), palbociclib (1), sorafenib+trametinib (1). We documented a minor response in one patient, a mixed response in 2, and a stable disease in 9. One patient with 459 somatic mutations and a MBD4 mutation had a partial durable response under Nivolumab. The median duration of the clinical benefit was 10 months (6-17). Median PFS was 3.33 months (95% CI: 0-7.21). It was significantly related to LDH and MYC status. Median OS was 12.47 months (95% CI: 7.33-17.63). It was significantly dependent on LDH, number of metastatic sites and MYC, in multivariate analysis. Overall, the targeted treatment had no significant influence on survival.

Conclusions: This precision oncology program was successful with more than half of the patients receiving a treatment based on molecular recommendations.

Legal entity responsible for the study: Charité Comprehensive Cancer Center, Berlin, Germany Max-Planck-Institut für molekulare Genetik, Berlin, Germany.

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1143P Nivolumab and ipilimumab (N+I) is active in patients (pts) with metastatic uveal melanoma (mUM) with extra-hepatic only involvement: Pooled analysis from 2 phase II trials

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Background: Approximately 40-50% of pts with UM will ultimately develop metastatic disease. There is currently no standard approach for mUM. Recently 2 phase II studies testing N+I have reported overall survivals exceeding 12 m without a great improvement in ORR (Piulats JM at ESMO 2018; Pelster M at ASCO 2019).

Methods: We performed a cohort study involving pts with mUM recruited in the two clinical trials testing N+I. The study used inverse probability of treatment propensity-score matching (PSM) using individualized patient data collected in the PUMMA study. This includes individualized patient data from 29 trials, and 912 patients, with the objective to determine benchmarks for OS.

Results: Raw and accelerated failure time models were fitted to assess the treatment effect on OS. Adjusting confounders were age, sex, LDH, M1 size and localization. In the primary analysis 87 pts were treated with N+I and 516 pts were treated with other systemic treatments. Because it is reported in other diseases that liver M1 perform worst with ICIs, a possible interaction between treatment and M1 localization was tested. In pts with extrahepatic metastasis, expected survival was $>$ 2.6 times higher in N+I treated pts (HR 0.38; 95%CI 0.15-0.94). In pts with liver-only metastases no differences were observed (HR 1.02; 95%CI 0.65-1.60), neither in pts with liver+extra-liver disease (HR 0.81; 95%CI 0.44-1.49). After applying PSM 85(N+I):170(PUMMA) pts were matched by age, sex, ECOG, LDH, and M1 localization. A statistically significant interaction between treatment and M1 localization was tested. In pts with only extrahepatic metastasis, expected survival was $>$ 3.2 times higher in N+I treated pts (HR 0.28; 95%CI 0.11-0.69). In pts with liver-only (HR 1.02; 95%CI 0.59-1.56) or liver+extra-liver (HR 1.05; 95%CI 0.54-2.03) no differences were observed in expected survival between treatments.

Conclusions: Up to 20% of pts with metastatic uveal melanoma present only extrahepatic disease and clearly benefits from N+I treatment. Biological samples from both studies are being analyzed to explain this observation. Liver metastases in mUM still remains a challenge and patients should be included in clinical trials.

Clinical trial identification: NCT02626962 - Spanish Melanoma Group (GEM) NCT01585194 - MD Anderson CRD42014006965 - Meta-analysis registration number - IRCI.

Legal entity responsible for the study: Spanish Melanoma Group - MD Anderson - IRCI.

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1144P Clinical predictors of therapeutic benefit from anti-PD1 immune checkpoint inhibitors (ICI) in patients (pts) with metastatic uveal melanoma

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Background: Metastatic uveal melanoma (mUM) is a rare disease, for which no systemic therapy has demonstrated overall survival (OS) benefit. Anti-PD1 +/- anti-CTLA4 ICI yields responses in 0-37% of mUM pts. This study evaluates the characteristics associated with ICI benefit in pts with mUM.

Methods: We performed a single-center retrospective cohort study of pts with mUM who received anti-PD1 +/- anti-CTLA4 ICI between 2014−19. Clinical characteristics, including baseline LDH and neutrophil to lymphocyte ratio (NLR) were abstracted from chart review. Treatment response (TR, any tumor shrinkage with no new growth) was determined by radiographic assessment and clinical progression was determined by physician assessment. Risk ratios (RR) and Fisher's exact test were used to make comparisons between groups. Univariable and multivariable Cox regression models were used to assess clinical progression free survival (cPFS) and OS.

Results: Of 75 mUM pts who received ICI, 55 (73%) had anti-PD1 and 20 (27%) had anti-PD1 + anti-CTLA4. Pt characteristics were: 35 (47%) male, median age 64 yrs (34-89), 56 (75%) had 0-1 prior systemic therapies, 28 (37%) with NLR $\geq$4, 30 (40%) with LDH $\geq$1.5xULN, 34 (45%) were diagnosed (dx) stage IV $<$2 years after initial dx. The median OS from time of ICI was 10.0mo. TR to ICI was observed in 9 (12.2%) of pts. Characteristics associated with cPFS and OS are indicated in the table. Pts (n=25) with $>$ 2yrs from initial dx to stage IV and LDH $<$1.5xULN were more likely to experience tumor shrinkage (RR 3.9; P=0.053), longer cPFS (5.8 vs. 2.4mo; HR 0.4; 95%CI 0.2-0.7; P=0.001) and longer OS (34.5 vs. 8.3mo; HR 0.3; 95%CI 0.1-0.5; P$<$0.001). Genomic analyses are ongoing.

Conclusions: Clinical features associated with ICI treatment benefit in mUM include: LDH$<$1.5xULN, NLR$<$4 and time from initial dx to stage IV $>$ 2years. In the absence of randomized controlled trials; real world evidence can be used to aid clinicians in optimizing treatment selection for mUM.

Table: 1144P

	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
cPFS						
Age >65	1.0	0.6-1.7	0.859	-	-	-
Male	0.8	0.5-1.3	0.389	-	-	-
>1 prior therapy	0.7	0.4-1.4	0.178	-	-	-
PD1+CTLA4 vs. PD1	1.1	0.6-1.8	0.789	-	-	-
LDH ≥1.5xULN	2.4	1.4-3.9	0.001	3.8	2.2-6.8	<0.001
Initial dx to stg IV <2yrs	1.8	1.1-2.9	0.016	2.2	1.3-3.7	0.002
NLR ≥4	1.6	1.0-2.5	0.076	1.9	1.1-3.2	0.014
OS						
Age >65	1.8	1.1-3.2	0.030	-	-	-
Male	1.0	0.6-1.7	0.982	-	-	-
>1 prior therapy	0.7	0.4-1.3	0.283	-	-	-
PD1+CTLA4 vs. PD1	1.2	0.6-2.3	0.588	-	-	-
LDH ≥1.5xULN	4.0	2.3-7.1	<0.001	4.4	2.4-7.9	<0.001
initial dx to stg IV <2yrs	1.9	1.1-3.3	0.016	2.5	1.4-4.3	0.002
NLR ≥4	1.7	1.0-2.9	0.060	2.1	1.2-3.7	0.014

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1145P Metabolic activity of liver metastases may predict survival in patients with metastatic uveal melanoma

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Background: Uveal melanoma (UM) has 50% chance of relapse after local treatment. Metastatic UM (MUM) mainly affects liver. MUM is fatal and to date no systemic treatment has improved survival. We aimed to explore liver metastases (M1) metabolic activity in MUM as a potential biomarker for survival.

Methods: We retrospectively analyzed newly diagnosed pts with MUM in our centre between 2004-2019. Patients were included if presented liver M1 by a liver-directed imaging study (CT or MRI) and simultaneously underwent a PET/TC at diagnosis. Metabolic activity was measured by PET/TC SUVmax. Other relevant clinical prognostic variables were also analyzed.

Results: A total of 51 patients were included. Median age was 62 years, 41% male and 22% ECOG PS ≥ 1. LDH, ALP and GGT were elevated in 49%, 37% and 57% pts, respectively. 37% presented extrahepatic disease, 33% had ≥30mm liver M1 and 35% had <2-y M1 free interval. Median liver M1 SUVmax was 8.5 (3 − 42.2). Interestingly, same size lesions presented a wide range of metabolic activity. SUVmax for < 30mm lesions varied from 2.6 to 22.3, and from 4.4 to 42.2 for larger lesions suggesting metabolic heterogeneity. Median OS was 17.3m (95% CI: 10.6 - 23.9). Using SUVmax≥ 8.5 as a cutoff value showed an AUC=0.66 according to time-dependent survival ROC analysis. Patients with SUVmax ≥ 8.5 showed 9.4m (95% CI: 6.4-12.3) OS, whereas for SUVmax < 8.5 the OS was 38.4m (95% CI: 21.4-55.5)($P < 0.0001$, HR=2.9). HR of SUVmax as a continuous variable was 1.068 (95% CI: 1.02-1.10; $P = 0.001$). That is, a 6.8% increase in hazard of death for each unit increase in SUVmax. For the multivariate analysis, 2 models were used. One with dichotomous SUVmax (≥ 8.5 vs <8.5) and other with continuous SUVmax. In both of them SUVmax remained significant. HR= 3.39 (95% CI: 1.56-7.35), P < 0.01 for SUVmax ≥ 8.5, and HR= 1.05 (95% CI: 1.01-1.03), p=0.001 for continuous SUVmax. Other clinical variables significant were < 2-y M1 free survival and diameter of largest M1.

Conclusions: Increased metabolic activity of liver metastases seems to be an independent predictor of survival. MUM is a heterogeneous disease and metabolic activity probably reflect a different intrinsic behaviour.

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1146P Rh-endostatin combined with chemotherapy and interferon in the treatment of oral mucosal melanoma without clinical cervical lymph node metastasis: A retrospective study in Chinese population

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Background: Oral Mucosal Melanoma (OMM) is the main subtype of melanoma in Chinese population. DTIC single-agent chemotherapy of OMM has a poor efficacy. Persistent angiogenesis is an important characteristic of OMM, Rh-endostatin (Endostar) can inhibit the angiogenesis of tumor and has a synergistic effect on chemotherapy.

Methods: Medical information of 68 patients diagnosed with Oral Mucosal Melanoma without clinical cervical lymph node metastasis in the department of Oral and Maxillofacial-Head and neck Oncology, Shanghai Ninth People's hospital, Shanghai Jiao Tong University School of Medicine from 2012 to 2017 were collected. The patients were divided into two groups, group A was treated with chemotherapy containing DTIC combined with interferon therapy, group B was added Endostar (30 mg/day, continuous infusion, day 1-7) at the time of chemotherapy.

Results: Baseline demographics and disease characteristics were generally balanced between the two treatment groups. The median age at diagnosis was 55 years old. Male patients compose 53% (36 out of 68 patients) of patients. At the time of treatment, 19 (28%) patients were diagnosed with T stage IV. The locations of OMM were commonly gingiva and palate, occasionally lip, tongue and buccal. The median OS and median DFS in group A is 37 (95% CI 32.41-41.59) months and 24 (95% CI 8.79-39.25) months respectively. The median OS and median DFS in group B is not reached. Patients treated with Endostar were less likely to develop local recurrence, regional recurrence and metastasis. No severe adverse event related to Endostar was reported.

Conclusions: Endostar combined with chemotherapy and interferon can significantly reduce the recurrence risk and improve the long-term survival rate in OMM without clinical cervical lymph node metastasis. Anti-tumor neovascularization therapy can be used as an effective adjuvant therapy strategy for OMM. Adverse reactions caused by Endostar have rarely been reported. Therefore, Endostar is more suitable for the combined treatment of OMM without clinical cervical lymph node metastasis.

Legal entity responsible for the study: Department of Oral and Maxillofacial-Head and Neck Oncology, Shanghai Ninth People' s Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

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1147P Primary ipilimumab/nivolumab immunotherapy followed by adjuvant nivolumab in locally advanced or oligometastatic melanoma: Preliminary results

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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. Recently, pathological response has been indicated as a surrogate of survival. 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, two centres study.

Methods: Treatment schedule consists in 4 neoadjuvant cycles of Ipilimumab 1 mg/kg and Nivolumab 3 mg/kg every 3 weeks, followed by surgery and adjuvant Nivolumab

480 mg every 4 weeks for 6 cycles. Primary objective is pathological complete remission (pCR) rate. Secondary objectives are: safety, feasibility and efficacy; health related quality of life; identification of molecular and immunological biomarkers of response and resistance (somatic genetic drivers, tumor mutational burden (TMB), mutational signatures, predicted neoantigens, germline HLA typing, somatic HLA mutations and liquid biopsy); degree of immune activation; evaluation of microbioma.

Results: From March 2019, 26 out of 35 pts were enrolled. In the ITT population (22 pts), 21 pts were stage III and 1 stage IV-M1b cutaneous melanoma; 17 pts concluded neoadjuvant therapy and received surgery; 4 pts concluded the adjuvant treatment. pCR was reached in 9/17 (52%), pathological partial remission in 4/17 (24%) and pathological no response (pNR) in 4/17 (24%) pts. With a median follow-up of 5 months, all pts are alive; one, with pNR at surgery, relapsed during adjuvant phase. In the neoadjuvant phase 4 pts (18%) developed G3-4 adverse events (AE): 2 transaminitis, 1 myocarditis and 1 asyntomatic CPK increase after 4, 3 and 2 cycles; 3 of them underwent to surgery after toxicity resolution. No G3-4 AE were observed during adjuvant phase.

Conclusions: Primary Ipilimumab/Nivolumab is effective and feasible, showing high pCR rate. Toxicity was superimposable to that already observed with this schedule. Longer follow-up is needed to assess a correlation between pathological response and survival. Translational data will be available and presented at ESMO.

Clinical trial identification: EudraCT: 2018-002172-40.

Legal entity responsible for the study: Pier Francesco Ferrucci.

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1148P Multiple primary melanoma incidence trends over five decades, a nationwide population-based study

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Background: Over the past decades many regions have experienced a steady increase in the incidence of cutaneous melanoma. Here, we report on incidence trends for subsequent primary melanoma.

Methods: In this nationwide population-based study, patients diagnosed with a first primary cutaneous melanoma reported to the Swedish Cancer Registry, were followed for up to ten years for a diagnosis of subsequent primary melanoma. Patients were grouped with patients diagnosed with first melanoma in the same decade (1960s, 1970s, 1980s, 1990s and 2000s, respectively). Frequencies, incidence rates (IRs), standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for second melanomas were calculated.

Results: 54,884 patients with melanoma were included and 2,469 were diagnosed, within ten years, with subsequent melanomas. Over the five decades there was a significant steady increase in the frequency, IR and SIR for second primary melanoma. E.g., in the 1960s cohort, <1% (1,0 per 1,000 person-years) had second primary melanoma and this rose to 6.4% (7.5 per 1,000 person-years) in the women and 7.9% (10.3 per 1,000 person-years) in the men in the 2000s cohort. This rise was seen, independent of age, sex, invasiveness or site of the melanoma. The SIR for second melanomas was 14.2 (95% CI 9.1-22.6) in women and 16.5 (95% CI 8.4-29.5) in men the 1960s and the SIR rose to 23.8 (95% CI 21.8-25.9) in women and 27.4 (95% CI 24.4-30.0) in men in the 2000s. Further, in patients diagnosed with a second melanoma, the frequency of those diagnosed with three or more melanomas increased significantly, from 0% in the 1960s to 18% in the 2000s.

Conclusions: This is the first study to evaluate and report on a rising trend for subsequent primary melanoma. The increase for second primary melanomas has occurred in parallel to the incidence increase for melanoma in the overall population, however the rise for second primaries has been steeper. Changes in sun exposure habits in the general population have likely caused individuals with constitutional vulnerability traits to become more inclined to develop multiple primary melanomas. Additional primary melanomas worsen the patients' survival and precautions are needed to turn this steep upgoing trend.

Legal entity responsible for the study: Hildur Helgadottir.

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1149P Validation of a model combining clinicopathologic risk factors and a gene expression profile to identify primary melanoma patients who can safely forgo sentinel lymph node biopsy

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Background: The sentinel lymph node biopsy (SLNB) procedure has gained importance now that primary cutaneous melanoma (PCM) patients with a positive sentinel lymph node are considered candidates for adjuvant systemic therapy. However, SLNB is an invasive procedure, and approximately 80% of patients lack nodal metastasis. Many SLNB negative patients are exposed to invasive surgery but enjoy no discernible therapeutic benefit. Therefore, there is a need for a non-invasive test to accurately identify PCM patients who may forgo the SLNB procedure due to low risk of nodal metastasis. Previously, a clinicopathological and gene expression profile model (CP-GEP model) has been developed to identify PCM patients who can safely forgo SLNB. Moreover, a validation of the CP-GEP model in a European cohort has been reported. Here, we describe the validation of the CP-GEP model in a US cohort.

Methods: We identified 162 patients who underwent SLNB at the Mayo Clinic or West Virginia University within 90 days of PCM diagnosis. Formalin-fixed paraffin-embedded diagnostic PCM biopsy tissue from all patients were analyzed using the CP-GEP model. The CP-GEP model combines Breslow thickness and patient age with the expression of eight genes to classify patients as CP-GEP High Risk or CP-GEP Low Risk for nodal metastasis.

Results: At diagnosis, the median patient age was 56 years (IQR, 41 to 69 years) and the median Breslow thickness was 1.9 mm (IQR, 0.9 to 2.1 mm). 62 of 162 patients (38.2%) presented with T1 melanoma while 58 of 162 patients (35.8%) presented with T2 melanoma. Overall, 19.8% of patients had a positive sentinel lymph node. In patients with stage T1 to T2 melanoma, the CP-GEP model achieved an SLNB reduction rate of 44.2% at a negative predictive value of 98.1%.

Conclusions: The CP-GEP model is a non-invasive and validated tool that is able to predict nodal metastasis in an US cohort that can be used to identify PCM patients who can safely forego SLNB. The CP-GEP model is a promising tool for patient care, preventing unnecessary surgery in a large group of patients.

Legal entity responsible for the study: Mayo Clinic.

Funding: SkylineDx.

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1150P Long-term outcomes of stage IIB-IV melanoma patients: Nationwide data from Norway

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Background: Population level data on the outcomes of melanoma patient survival by TNM stage are scarce. This study aimed to investigate the characteristics and outcomes of Norwegian cutaneous melanoma patients with stage IIB-IV. Patients included in the study should be fully resected and stages III and IV eligible for adjuvant therapy.

Methods: For this retrospective cohort study, all patients with cutaneous melanoma (ICD-10:C43), diagnosed between Jan-2008 to Dec-2018 with AJCC8 TNM stage IIB-IV

(stage IV patients with no evidence of surgery were excluded) were identified in the population based Cancer Registry of Norway. The primary outcome of interest was overall survival (OS). The OS experience of the cohort was evaluated using Kaplan-Meier and Cox Proportional Hazards methods.

Results: A total of 4,339 patients were included; 57.9% male, 42.1% female, median age 72 (IQR 60-82). Stage IIB/C patients made up half of the cohort: IIB 35.7% and IIC 17.7%. Additional stages included IIIA 4.0%, IIIB 8.2%, IIIC 18.8%, IIID 2.7% and IV 13%. A male predominance was consistent across stages but average age distribution varied with IIC patients appearing older (IIB vs IIC: 71.9 vs 78.5) and IIIA younger (IIB vs IIIA: 71.9 vs 58.4) compared to IIB. OS varied by stage with 3-year OS in IIB 74.5%, IIC 48.7%, IIIA 91.5%, IIIB 76.7% IIIC 63.1% IIID 55.4% and IV 63.7%. There was an overall trend for higher OS in stage IIIA in comparison to IIB. This trend persisted in multivariable cox models (IIIA vs IIB, HR 0.63, 95% CI 0.41-0.97, p=0.037) adjusting for potential confounders including age, sex and anatomical site of disease. Trends in survival were explored further in analyses focusing on cancer-specific mortality. Risk of cancer specific mortality in IIC patients was elevated in comparison to IIB (HR 2.23, 95% CI 1.84-2.70, p=<0.001), however, there was no difference between IIIA and IIB (HR 0.90, 95% CI 0.55-1.48, p=0.682).

Conclusions: OS for stage II melanoma patients, and particularly IIC, is poor and in some cases worse than patients with more advanced stage melanoma. Our data highlight a high and unmet need amongst the stage II population for effective adjuvant treatment options.

Legal entity responsible for the study: The Authors.

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1151P Trends in melanoma mortality in Brazil: A 20-year registry-based study

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Background: A substantial increase in melanoma (MM) incidence has been consistently observed worldwide over the past decades. MM mortality rates, however, remained stable or declined over the past years in most countries. Given the paucity of MM mortality data in Brazil, we sought to characterize MM mortality trends in southeastern Brazil and its relationship with demographic variables.

Methods: A cross-sectional registry-based analysis was conducted to describe MM mortality trends in the State of Sao Paulo (Brazil) from 1996 to 2016. Melanoma-related death records, including gender and age were collected from SEADE Foundation's database, an official entity charged with generating statistical data for the State of Sao Paulo. The annual percentage change (APC) was calculated to identify mortality trends over the period. Trend analysis was carried out by linear regression and an increase or decrease in trend was considered statistically significant when p-value < 0.05.

Results: From 1996 to 2016, 8217 deaths from melanoma were recorded in the State of São Paulo, Brazil. Average annual mortality due to melanoma was 1.05/100,000 (1.17/100,000 for males and 0.93/100,000 for females). Male mortality from melanoma exceeded female rates throughout the period since 1999. An increasing MM mortality trend was detected among males, regardless of age (APC 1.72%, $p < 0.001$), and was more pronounced for the for males older than 60 years (APC 2.63%, $p < 0.001$). MM mortality rates have also increased for the age group older than 60 years (APC 1.11%, $p < 0.001$), regardless of gender. A non-statistically significant increase in the overall MM mortality rate was observed over the 20-year period analyzed (APC 0.36%, $p = 0.4$).

Conclusions: Our data suggest a stable MM mortality over the last two decades for the general population. However, a significant increase in MM mortality rates has been demonstrated among males and in the population over 60 years old.

Legal entity responsible for the study: The authors.

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Disclosure: G. Nader Marta: Travel/Accommodation/Expenses: Bayer; Travel/Accommodation/Expenses: Roche. R. Ramella Munhoz: Honoraria (self): Bristol-Myers Squibb; Honoraria (self), Advisory/Consultancy: Merck Sharp Dohme; Honoraria (self), Advisory/Consultancy: Novartis; Honoraria (self), Advisory/Consultancy: Roche. O. Feher: Speaker Bureau/Expert testimony, Research grant/Funding (institution), Travel/Accommodation/Expenses: Roche. All other authors have declared no conflicts of interest.

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1152P Influence of dietary and physical exercise habits on the melanoma risk: A case-control study

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Background: Melanoma is a complex disease caused by the interaction of genetic, phenotypic and environmental factors. Early diagnosis remains the best strategy to fight the disease. Thus, it is necessary to identify individuals with a higher risk of developing melanoma. Some studies link obesity to the development of cancer, but evidence for its influence on melanoma is limited. This study aimed to assess whether dietary and physical activity habits are associated with melanoma risk.

Methods: A case-control study was performed with 130 melanoma patients from Hospital Clínic of Barcelona and 166 healthy individuals from the same population, similar in age and sex distribution. Data were obtained through a questionnaire about epidemiological characteristics; dietary restrictions; weekly consumption of specific foods; main cooking methods; and frequency and intensity of physical exercise.

Results: In our cohort, we have not found an association between BMI and melanoma. Restriction of sugary foods (OR 0.12, 95% CI 0.05-0.27; $P<0.001$) and an intake >3 times a week of cereals rich in fiber (OR 0.59, 95% CI 0.37-0.94; $P=0.027$) and fruits and vegetables rich in vitamin E (OR 0.34, 95% CI 0.13-0.91; $P=0.026$) conferred a protective effect against melanoma. On the contrary, restriction of dairy products (OR 2.66, 95% CI 1.32-5.36; $P=0.005$) and a high intake of processed meats (OR 2.52, 95% CI 1.57-4.04; $P<0.001$) and carotenoid-rich fruits and vegetables (OR 2.39, 95% CI 1.15-4.97; $P=0.018$) were associated with a higher risk of melanoma. Moreover, melanoma patients used unhealthy cooking methods (deep-frying, battering) more often than controls, especially for eggs (49.1% vs. 30.1%; $P=0.001$), white fish (17.1% vs. 7.5%; $P=0.014$) and blue fish (23.9% vs. 9.6%; $P=0.002$). Besides, we observed a protective effect not for practicing physical exercise itself but for its intensity ($P<0.001$) and its frequency, the latter restricted to females ($P=0.033$).

Conclusions: Our study confirms that multiple dietary factors and exercise habits may influence the risk of developing melanoma. The identification of protective habits against melanoma would allow new prevention strategies that would improve public health beyond individual benefit.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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1153TiP A phase II, open label study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with advanced unresectable/metastatic Merkel cell carcinoma progressing on anti-PD-(L)1 antibody therapy: The MERKLIN 2 study

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Background: Merkel cell carcinoma (MCC) is a rare but highly aggressive human skin cancer that is often caused by the Merkel cell polyomavirus or extended exposure to sunlight. Historically, first-line treatment options for patients with advanced unresectable/metastatic MCC have been rare. However, 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 to previous anti-PD-(L)1 antibody monotherapy ultimately leaving these patients with only limited treatment options. Recent preclinical data suggest that the small molecule selective class I histone deacetylase inhibitor (HDACi) domatinostat is able to overcome critical mechanisms of MCC resistance to checkpoint inhibitors. These escape mechanisms include the epigenetic downregulation of the antigen processing and presentation machinery, hence treatment with domatinostat is thought to favorably modulate the tumor environment therefore allowing a reintroduction of anti-PD-(L)1 therapy for an improved and sustained clinical benefit.

Trial design: The study 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 advanced unresectable/metastatic MCC that are

progressing on previous anti-PD-(L)1 therapy. A total of 40 patients will be enrolled in up to 40 clinical study sites in Europe and USA. Anti-tumor activity will be primarily assessed by the Objective Response Rate (ORR) defined as the percentage of patients having a confirmed CR or PR according to RECIST v1.1 in an exploratory analysis. Secondary objectives include additional efficacy assessments, safety, quality of life (HRQoL) and pharmacokinetics of domatinostat in combination with avelumab. Correlative aims include evaluating biomarkers for association with clinical benefit.

Clinical trial identification: NCT04393753.

Legal entity responsible for the study: 4SC AG.

Funding: 4SC AG.

Disclosure: A.C.J. van Akkooi: Honoraria (institution), Advisory/Consultancy: Amgen; Honoraria (institution), Advisory/Consultancy: Bristol- Myers Squibb; Honoraria (institution), Advisory/Consultancy: Novartis; Honoraria (institution), Advisory/Consultancy: MSD; Honoraria (institution), Advisory/Consultancy: Merck KgAa/ Pfizer; Honoraria (institution), Advisory/Consultancy: Sanofi; Honoraria (institution), Advisory/Consultancy: 4SC AG; Research grant/Funding (institution): Amgen; Research grant/Funding (institution): Novartis; Research grant/Funding (institution): Merck KGaA/ Pfizer. P.A. Ascierto: Research grant/Funding (institution): Bristol-Myers Squibb; Research grant/Funding (institution): Roche/Genentech; Research grant/Funding (institution): Array; Shareholder/Stockholder/Stock options: PrimeVax; Honoraria (self), Advisory/Consultancy: 4SC AG; Honoraria (self), Advisory/Consultancy: Immunocore; Honoraria (self), Advisory/Consultancy: Sandoz; Honoraria (self), Advisory/Consultancy: Ultimovacs; Honoraria (self), Advisory/Consultancy: Idera; Honoraria (self), Advisory/Consultancy: Sanofi; Honoraria (self), Advisory/Consultancy: Sun Pharma; Honoraria (self), Advisory/Consultancy: Syndax; Honoraria (self), Advisory/Consultancy: AstraZeneca; Honoraria (self), Advisory/Consultancy: MedImmune; Honoraria (self), Advisory/Consultancy: Genmab; Honoraria (self), Advisory/Consultancy: Newlinks Genetics; Honoraria (self), Advisory/Consultancy: Incyte; Honoraria (self), Advisory/Consultancy: Pierre Fabre; Honoraria (self), Advisory/Consultancy: Merck Serono; Honoraria (self), Advisory/Consultancy: Array; Honoraria (self), Advisory/Consultancy: Novartis; Honoraria (self), Advisory/Consultancy: Merck Sharp & Dohme; Honoraria (self), Advisory/Consultancy: Roche/Genentech; Honoraria (self), Advisory/Consultancy: Bristol-Myers Squibb; Honoraria (self), Advisory/Consultancy: Nektar; Honoraria (self), Advisory/Consultancy: Alkermes; Honoraria (self), Advisory/Consultancy: Italfarmaco; Travel/Accommodation/Expenses: Merck Sharp & Dohme. J.C. Becker: Speaker Bureau/Expert testimony: Amgen; Speaker Bureau/Expert testimony: Pfizer; Speaker Bureau/Expert testimony: Merck KGaA; Speaker Bureau/Expert testimony: Recordati; Speaker Bureau/Expert testimony: Sanofi; Honoraria (institution), Advisory/Consultancy: Boehringer Ingelheim; Honoraria (institution), Advisory/Consultancy: eTheRNA; Honoraria (institution), Advisory/Consultancy: In ProTher; Honoraria (institution), Advisory/Consultancy: Pfizer; Honoraria (institution), Advisory/Consultancy: 4SC AG; Honoraria (institution), Advisory/Consultancy: Sanofi; Research grant/Funding (institution): Bristol-Myers Squibb; Research grant/Funding (institution): Merck KgAa; Research grant/Funding (institution): HTG; Research grant/Funding (institution): IQVIA; Research grant/Funding (institution): Alcedis. P. Nathan: Honoraria (self), Advisory/Consultancy: 4SC; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Novartis; Honoraria (self), Advisory/Consultancy, Travel/Accommodation/Expenses: BMS; Honoraria (self), Advisory/Consultancy, Speaker Bureau/Expert testimony: Merck; Honoraria (self), Advisory/Consultancy: Pfizer; Honoraria (self), Advisory/Consultancy: Ipsen; Honoraria (self), Advisory/Consultancy, Research grant/Funding (institution): Immunocore. P. Nghiem: Honoraria (self), Advisory/Consultancy: Pfizer; Honoraria (self), Advisory/Consultancy: EMD Serono; Honoraria (self), Advisory/Consultancy: UpToDate; Advisory/Consultancy: 4SC AG; Research grant/Funding (self): EMD Serono; Research grant/Funding (self): Bristol-Myers Squibb; Research grant/Funding (self): Amgen; Research grant/Funding (self): Kadmon; Research grant/Funding (self): Pfizer; Research grant/Funding (self): Syndax; Research grant/Funding (self): Incyte; Research grant/Funding (self): AstraZeneca; Travel/Accommodation/Expenses: Sanofi; Travel/Accommodation/Expenses: Genzyme & Regeneration; Travel/Accommodation/Expenses: Merck Sharp & Dohme; Travel/Accommodation/Expenses: Amgen. U. Ostermeier, P.G. Reimann, F. Hermann: Full/Part-time employment: 4SC AG.

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1154TiP A randomized, prospective, multicenter study to assess the impact of early detection of asymptomatic brain metastases (mets) vs standard follow-up on symptomatic brain mets free survival (SBMFS) in pts with previously untreated, unresectable or metastatic melanoma (MM)

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Background: In patients with MM, brain mets are an indication of poor prognosis, with short OS, PFS and neurological deterioration. Median OS from diagnosis of brain mets is in the range of 17—22 weeks (w), suggesting a crucial need for treatments that can control central nervous system (CNS) progression. Until recently, the management of MM brain mets has included surgical resection, stereotactic radiosurgery, whole-brain radiation therapy, and/or cytotoxic chemotherapy, without a clear change in the natural history of the disease. New drug therapies based on combined BRAF+MEK inhibition for pts BRAF V600 mutant and immunotherapies such as CTLA-4 inhibitors and PD-1 inhibitors, have shown promising results in the setting of MM, leading to median OS of 14-23 months (m). We hypothesize that the early diagnosis of brain mets will improve the symptomatic brain mets free survival (SBMFS) in pts with previously untreated, unresectable or MM by guiding effective treatment options.

Trial design: This is a randomized, open-label, multi-center, phase II study to assess the impact of early detection of asymptomatic brain mets vs standard follow-up on SBMFS in patients with previously untreated, unresectable or MM. A total of 122 pts will be randomized 1:1 to (i) experimental group: serial brain magnetic resonance imaging (MRI); or (ii) control group: standard follow-up. The stratification factors used for randomization are: LDH (normal vs. above upper normal limit); and BRAF V600 (mutated vs. wild-type). Pts in experimental group will undergo brain MRI scans every 16 w or sooner if the patient presents neurological symptoms. Patients in control group will receive neurological examination as per standard of care and CNS imaging will be performed at the time of neurological symptoms/signs. The primary endpoint is SBMFS. The study has 80% power to detect an improvement of 6m in median SBMFS using 80% confidence interval. The follow-up visits in both groups will be every 16 w (+/- 7 d) with a maximum follow-up of 36 m for OS. Recruitment period was estimated in 18 m, with total study duration of 42 m.

Clinical trial identification: CA209-7J3/ VHIO19pr001.

Legal entity responsible for the study: VHIO; Vall d'Hebron Insitute of Oncology.

Funding: Bristol-Myers Squibb.

Disclosure: E. Munoz Couselo: Advisory/Consultancy, Speaker Bureau/Expert testimony: Roche; Advisory/Consultancy, Speaker Bureau/Expert testimony: Bristol-Myers Squibb; Advisory/Consultancy, Speaker Bureau/Expert testimony: MSD; Advisory/Consultancy, Speaker Bureau/Expert testimony: Pierre-Fabre; Advisory/Consultancy, Speaker Bureau/Expert testimony: Sanofi; Advisory/Consultancy, Speaker Bureau/Expert testimony: Merck. G. Villacampa Javierre: Speaker Bureau/Expert testimony: Merck Sharp; Speaker Bureau/Expert testimony: Dohme. All other authors have declared no conflicts of interest.

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1155TiP Pan-tumour study CheckMate 8TT for long-term follow-up of cancer survivors who have participated in trials investigating nivolumab

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Background: Nivolumab (NIVO), a programmed death receptor-1 (PD-1)—blocking antibody that releases PD-1 pathway-mediated inhibition of anti-tumor immune responses, is approved for the treatment of multiple cancers. Long-term safety data and collection of overall survival (OS) events could inform the toxicity profile regarding late-onset adverse events (AEs) including immune-related AEs (irAEs) and increase understanding of the impact of underlying disease and comorbidity on long-term survivorship issues in NIVO-treated patients.

Trial design: CheckMate 8TT is a phase II, open-label, pan-tumor, continuation study with a novel rollover design investigating long-term safety of cancer survivors participating in NIVO trials. This study provides an opportunity for uninterrupted NIVO treatment for patients receiving NIVO monotherapy in the parent study, as well as long-term follow-up of those who have completed NIVO therapy. Inclusion criteria include eligibility for NIVO as per parent protocol and patients who are currently within, or have completed, the follow-up phase of the parent study (completed treatment, progressed on treatment, or on subsequent therapy). Exclusion criteria include ineligibility for NIVO as per parent protocol, investigator assessment that continued treatment is not in the best interest of the patient due to lack of clinical benefit from NIVO, AEs, laboratory abnormalities, and/or concomitant illness. There are no exclusion criteria for survival follow-up. For eligible patients, NIVO (480 mg IV every 4 wks or 240 mg IV every 2 wks, as per investigator's choice) will be continued until progression, unacceptable toxicity, withdrawal of consent, or parent protocol—determined end of treatment. The imaging schedule is per the investigator's determination and thus mirrors real-world use. The primary objective is evaluation of long-term safety of NIVO in patients on treatment and in follow-up as measured by the incidence of AEs. Long-term efficacy, including OS, from the beginning of treatment in the parent study is an exploratory objective. Additional analyses will potentially include patient demographics, comorbidities, hypersensitivity reactions, and irAE/AE outcomes.

Clinical trial identification: NCT03899155.

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Research grant/Funding (institution): Zymeworks; Speaker Bureau/Expert testimony: Taiho. E. Kalinka: Honoraria (self): Bristol-Myers Squibb; Honoraria (self): Merck Sharp & Dohme; Honoraria (self): Roche; Honoraria (self): AstraZeneca. F. Hosein: Shareholder/Stockholder/Stock options, Full/Part-time employment: Bristol-Myers Squibb. J. Li: Shareholder/Stockholder/Stock options, Full/Part-time employment: Bristol-Myers Squibb. N. Khushalani: Advisory/Consultancy, Research grant/Funding (institution), Non-remunerated activity/ies: Bristol-Myers Squibb; Advisory/Consultancy, Research grant/Funding (institution): Merck; Research grant/Funding (institution): Celgene; Research grant/Funding (institution): Novartis; Advisory/Consultancy, Research grant/Funding (institution): Huya Biosciences; Research grant/Funding (institution): GlaxoSmithKline; Advisory/Consultancy, Research grant/Funding (institution), Non-remunerated activity/ies: Regeneron; Research grant/Funding (institution): Amgen; Advisory/Consultancy: Array; Advisory/Consultancy: Genentech; Advisory/Consultancy, Non-remunerated activity/ies: Sanofi; Advisory/Consultancy: EMD Serono; Advisory/Consultancy: Jounce; Advisory/Consultancy: Immunocore; Advisory/Consultancy, Data Safety Monitoring Board: AstraZeneca; Advisory/Consultancy, Data Safety Monitoring Board: Incyte; Shareholder/Stockholder/Stock options: Bellicum; Advisory/Consultancy: TransEnterix; Advisory/Consultancy: Amarin; Advisory/Consultancy: Mazor Robotics. All other authors have declared no conflicts of interest.

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