9500 **Oral Abstract Session**

Crossover and rechallenge with pembrolizumab in recurrent patients from the EORTC 1325-MG/Keynote-054 phase 3 trial, pembrolizumab versus placebo after complete resection of high-risk stage III melanoma.

Alexander M. Eggermont, Andrey Meshcheryakov, Victoria Atkinson, Christian U. Blank, Mario Mandalà, Georgina V. Long, Catherine Barrow, Anna Maria Di Giacomo, Rosalie Stephens, Shahneen Kaur Sandhu, Ragini Reiney Kudchadkar, Pablo L. Ortiz-Romero, Inge Marie Svane, Alexander Christopher Jonathan Van Akkooi, Clemens Krepler, Nageatte Ibrahim, Sandrine Marreaud, Michal Kicinski, Stefan Suciu, Caroline Robert; Princess Máxima Center, Utrecht, Netherlands; NN Blokhin Cancer Research Center, Moscow, Russian Federation; Princess Alexandra Hospital, Gallipoli Medical Research Foundation, University of Queensland, Woolloongabba, QLD, Australia; Netherlands Cancer Institute (NKI-AVL), Department of Medical Oncology, Amsterdam, Netherlands; Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; Wellington Blood and Cancer Centre, Wellington, New Zealand; Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; Auckland City Hospital, Auckland, New Zealand; Peter MacCallum Cancer Center, Melbourne, VIC, Australia; Winship Cancer Institute of Emory University, Atlanta, GA; Hospital Universitario 12 de Octubre, Medical School, University Complutense, Madrid, Spain; Herlev Gentofte Hospital, Herlev, Denmark; Netherlands Cancer Institute (NKI-AVL), Amsterdam, Netherlands; Merck & Co., Inc., Kenilworth, NJ; EORTC Headquarters, Brussels, Belgium; Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France

Background: The phase 3 double-blind EORTC 1325/KEYNOTE-054 trial evaluated pembrolizumab (pembro) vs placebo in stage III cutaneous melanoma patients (pts) with complete resection of lymph nodes. Pembro improved RFS (hazard ratio [HR] 0.57) and DMFS (HR 0.60) (Eggermont, NEJM 2018, TLO 2021). In the pembro group, the incidence of immune related AE (irAE) grade 1-5 was 37%, and of grade 3-5 was 7%. We present the safety profile, response rate and PFS for the subset of pts who had a recurrence and crossed over or were rechallenged with pembrolizumab, within protocol. **Methods:** Pts were randomized to receive iv. pembro 200 mg (N=514) or placebo (N=505) every 3 weeks for a total of 18 doses (~1 year). Upon recurrence with no brain metastases, pts with an ECOG PS 0-2 were eligible to enter part 2 of the study, i.e. to receive pembro 200 mg iv. every 3 weeks for a maximum of 2 years, for crossover (those who received placebo) or rechallenge (those who recurred ≥6 months after completing one year of pembro therapy). Treatment was stopped in case of disease progression (RECIST 1.1) or unacceptable toxicity. **Results:** At the clinical cut-off (16-Oct-2020), 298 (59%) pts had a disease recurrence in the placebo group; 155 pts participated in the crossover part 2 of the trial. A total of 297 (58%) pts completed the 1-yr pembro adjuvant treatment, of whom 47 had a recurrence ≥6 mths from the stop of treatment and 20 entered in the rechallenge part of the trial. Among 175 pts who started pembro in Part 2, 160 discontinued due to completion of therapy (N=24), disease progression (N=88), toxicity (N=20), investigator's decision (N=21), or other reason (N=7); 15 pts were still on-treatment. Results for the 2 groups are provided in the table. The median number of doses was 12 and 5.5, respectively (resp), and the median follow-up was 41 and 19 mts, resp. Among the 175 pts, 51 (29%) had a grade 1-4 irAE (by group: 47 [30%] and 4 [20%] resp) and 11 (6%) a grade 3-4 irAE. **Conclusions:** Pembrolizumab treatment after crossover yielded a 39% ORR in evaluable pts and an overall 3-yr PFS of ~32%, but after rechallenge the efficacy was lower. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA The median PFS (95% CI) from start of Part 2 was 14 (5-27) and 8 (5-15) mts for stage III-resected and III/IV various, resp. Among the 80 stage IV crossover pts with evaluable disease, 31 (39%) had an objective response: 14 (18%) CR, 17 (21%) PR. The 2-yr PFS rate from response was 69% (95% CI 48-83%). For these 80 pts, the median PFS was 6.1 mts and the 3-yr PFS rate was 31% (95% CI 21-41%). Among 9 stage IV rechallenged pts with an evaluable disease, 1 (11%) reached CR, 3 had SD and 5 PD.Clinical trial information: NCT02362594.

	Crossover (N=155)	Rechallenge (N=20)
Stage at baseline of Part 2, n		
III-resected	50	7
III/IV various	105	13
IV unresected	83	9
III-C unresected	10	
IV resected	12	4
PFS events in Part 2, n	103	12
Median PFS (95% CI), mts	8.5 (5.7-15.2)	4.1 (2.6-NE)
3-yr PFS rate (95% CI), %	32 (25-40)	NE

9501 **Oral Abstract Session**

Final analysis of overall survival (OS) and relapse-free-survival (RFS) in the intergroup S1404 phase III randomized trial comparing either high-dose interferon (HDI) or ipilimumab to pembrolizumab in patients with high-risk resected melanoma.

Kenneth F. Grossmann, Megan Othus, Sapna Pradyuman Patel, Ahmad A. Tarhini, Vernon K. Sondak, Teresa M. Petrella, Thach-Giao Truong, Nikhil I. Khushalani, Justine Vanessa Cohen, Elizabeth Iannotti Buchbinder, Kari Lynn Kendra, Pauline Funchain, Karl D. Lewis, Bartosz Chmielowski, Hongli Li, James Moon, Krishna Soujanya Gunturu, Zeynep Eroglu, John M. Kirkwood, Antoni Ribas; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; SWOG Statistical Center, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Moffitt Cancer Center, Tampa, FL; Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Kaiser Permanente, Dept of Medical Oncology, Vallejo, CA; Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center, Tampa, FL; Massachusetts General Hospital, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; The Ohio State University Comprehensive Cancer Center, Department of Internal Medicine, Columbus, OH; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; University of Colorado Comprehensive Cancer Center, Aurora, CO; Division of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA; SWOG, Seattle, WA; Southwest Oncology Group Statistical Center, Seattle, WA; Lahey Hospital and Medical Center, Burlington, MA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of Pittsburgh Medical Center, Pittsburgh, PA; University of California Los Angeles, Los Angeles, CA

Background: We assessed whether or not adjuvant pembrolizumab given over 1 year would improve OS and RFS in comparison to high dose ipilimumab (ipi10) or HDI - the two FDA-approved adjuvant treatments for high risk resected melanoma at the time of study design. **Methods:** Patients age 18 or greater with resected stages IIIA(N2), B, C and IV were eligible. Patients with CNS metastasis were excluded. At entry, patients must have had complete staging and adequate surgery to render them free of melanoma including completion lymph node dissection for those with sentinel node positive disease. Prior therapy with PD-1 blockade, ipilimumab or interferon was not allowed. Two treatment arms were assigned based on stratification by stage, PD-L1 status (positive vs. negative vs. unknown), and intended control arm (HDI vs. Ipi10). Patients enrolled between 10/2015 and 8/2017 were randomized 1:1 to either the control arm [(1) interferon alfa-2b 20 MU/m2 IV days 1-5, weeks 1-4, followed by 10 MU/m2/d SC days 1, 3, and 5, weeks 5-52 (n=190), or (2) ipilimumab 10 mg/kg IV q3w for 4 doses, then q12w for up to 3 years (n=465)], or the experimental arm [pembrolizumab 200 mg IV q3w for 52 weeks (n=648)]. The study had three primary comparisons: 1) RFS among all patients, 2) OS among all patients, 3) OS among patients with PD-L1+ baseline biopsies. Results: 1,426 patients were screened and 1,345 patients were randomized with 11%, 49%, 34%, and 6% AJCC7 stage IIIA(N2), IIIB, IIIC and IV, respectively. This final analysis was performed per-protocol 3.5 years from the date the last patient was randomized, with 512 RFS and 199 OS events. The pembrolizumab group had a statistically significant improvement in RFS compared to the control group (pooled HDI and ipi10) with HR 0.740 (99.618% CI, 0.571 to 0.958). There was no statistically signifcant improvement in OS in the 1,303 eligible randomized overall patient population with HR 0.837 (96.3% CI, 0.622 to 1.297), or among the 1,070 (82%) patients with PD-L1 positive baseline biopsies with HR 0.883 (97.8% CI, 0.604 to 1.291). Gr 3/4/5 event rates were as follows: HDI 69/9/0%, ipi10 43/5/0.5% and pembrolizumab 17/2/0.3%. **Conclusions:** Pembrolizumab improves RFS but not OS compared to HDI or ipi10 in the adjuvant treatment of patients with high-risk resected melanoma. Pembrolizumab is a better tolerated adjuvant treatment regimen than HDI or Ipi10. Support: NIH/NCI NCTN grants CA180888, CA180819, CA180820, CA180863; and in part by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Editorial Acknowledgement: With special thanks to Elad Sharon, MD, MPH, and Larissa Korde, MD, MPH. National Cancer Institute, Investigational Drug Branch, for their contributions to this trial, as well as Nageatte Ibrahim, MD, and Sama Ahsan, MD Merck. Clinical trial information: NCT02506153. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

9502 **Oral Abstract Session**

Neoadjuvant and adjuvant nivolumab (nivo) with anti-LAG3 antibody relatlimab (rela) for patients (pts) with resectable clinical stage III melanoma.

Rodabe Navroze Amaria, Michael A. Postow, Michael T. Tetzlaff, Merrick I. Ross, Isabella Claudia Glitza, Jennifer Leigh McQuade, Michael K.K. Wong, Jeffrey E. Gershenwald, Ryan Goepfert, Emily Zhi-Yun Keung, Sarah B. Fisher, Denai R. Milton, Sapna Pradyuman Patel, Adi Diab, Lauren Simpson, Michael A. Davies, Jennifer Ann Wargo, Elizabeth M. Burton, Charlotte Eielson Ariyan, Hussein Abdul-Hassan Tawbi; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY; UCSF, San Francisco, CA; University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX

Background: Neoadjuvant therapy (NT) for pts with clinical stage III melanoma remains an active area of research interest. Recent NT trial data demonstrates that achieving a pathologic complete response (pCR) correlates with improved relapse-free (RFS) and overall survival (OS). Checkpoint inhibitor (CPI) NT with either high or low dose ipilimumab and nivolumab regimens produces a high pCR rate of 30-45% but with grade 3-4 toxicity rate of 20-90%. In metastatic melanoma (MM), the combination of nivo with rela (anti Lymphocyte Activation Gene-3 antibody) has demonstrated a favorable toxicity profile and responses in both CPI-naïve and refractory MM. We hypothesized that NT with nivo + rela will safely achieve high pCR rates and provide insights into mechanisms of response and resistance to this regimen. **Methods:** We conducted a multi-institutional, investigator-initiated single arm study (NCT02519322) enrolling pts with clinical stage III or oligometastatic stage IV melanoma with RECIST 1.1 measurable, surgically-resectable disease. Pts were enrolled at 2 sites and received nivo 480mg IV with rela 160mg IV on wks 1 and 5. Radiographic response (RECIST 1.1) was assessed after completion of NT; surgery was conducted at wk 9 and specimens were assessed for pathologic response per established criteria. Pts received up to 10 additional doses of nivo and rela after surgery, with scans every 3 mo to assess for recurrence. The primary study objective was determination of pCR rate. Secondary objectives included safety, radiographic response by RECIST 1.1, event-free survival (EFS), RFS, and OS analyses. Blood and tissue were collected at baseline, at day 15, day 28, and at surgery for correlative analyses. **Results:** A total of 30 pts (19 males, median age 60) were enrolled with clinical stage IIIB/IIIC/IIID/IV (M1a) in 18/8/2/2 pts, respectively. 29 pts underwent surgery; 1 pt developed distant metastatic disease while on NT. pCR rate was 59% and near pCR ($<$ 10% viable tumor) was 7% for a major pathologic response (MPR, pCR + near pCR) of 66%. 7% of pts achieved a pPR (10-50% viable tumor) and 27% pNR ($\geq$50% viable tumor). RECIST ORR was 57%. With a median follow up of 16.2 mos, the 1 -year EFS was 90%, RFS was 93%, and OS was 95%. 1-year RFS for MPR was 100% compared to 80% for non-MPR pts (p = 0.016). There were no treatment related gr 3/4 AEs that arose during NT; 26% of pts had a gr 3/4 AE that began during adjuvant treatment. **Conclusions:** Neoadjuvant and adjuvant treatment with nivo and rela achieved high pCR and MPR rates with a favorable toxicity profile in the neoadjuvant and adjuvant settings. Pts with MPR had improved outcomes compared to non-MPR pts. Translational studies to discern mechanisms of response and resistance to this combination are underway. Clinical trial information: NCT02519322. Research Sponsor: Bristol Myers Squibb, MD Anderson Melanoma Moonshot Program.

9503 **Oral Abstract Session**

Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: Primary phase III results from RELATIVITY-047 (CA224-047).

Evan J. Lipson, Hussein Abdul-Hassan Tawbi, Dirk Schadendorf, Paolo Antonio Ascierto, Luis Matamala, Erika Castillo Gutiérrez, Piotr Rutkowski, Helen Gogas, Christopher D. Lao, Juliana Janoski de Menezes, Stéphane Dalle, Ana Maria Arance, Jean-Jacques Grob, Shivani Srivastava, Mena Abaskharoun, Katy L. Simonsen, Bin Li, Georgina V. Long, F. Stephen Hodi; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Dermatology, University of Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany; Istituto Nazionale Tumori Fondazione "G. Pascale", Naples, Italy; Department of Oncology, Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile; Department of Oncology, Instituto Nacional del Cancer, Santiago, Chile, Santiago, Chile; FAICIC Clinical Research, Veracruz, Mexico; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; National and Kapodistrian University of Athens, Athens, Greece; Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI; Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; Unit of Dermatology, Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Aix-Marseille University, CHU Timone, Marseille, France; Bristol-Myers Squibb, Princeton, NJ; Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Dana-Farber Cancer Institute, Boston, MA

Background: Immune checkpoint inhibitor therapy has revolutionized the treatment of patients with advanced melanoma. However, novel combinations are needed to optimize the benefit-risk profile. Lymphocyte-activation gene 3 (LAG-3) regulates an immune checkpoint pathway, which inhibits T-cell activity, and is upregulated in many tumor types including melanoma. Relatlimab (RELA), a human IgG4 LAG-3-blocking antibody, restores effector function of exhausted T cells. RELA in combination with nivolumab (NIVO; anti-programmed death [PD]-1) modulates potentially synergistic immune checkpoint pathways and can enhance antitumor immune responses. RELATIVITY-047 is a global, randomized, double-blind, phase II/III study evaluating a novel immune checkpoint inhibitor combination of RELA+NIVO as a fixed-dose combination (FDC) treatment in first-line advanced melanoma. **Methods:** Patients with previously untreated advanced melanoma were randomized 1:1 to receive RELA 160 mg + NIVO 480 mg FDC intravenously (IV) every 4 weeks (Q4W) or NIVO monotherapy 480 mg IV Q4W, stratified by LAG-3 expression, programmed death ligand 1 expression, *BRAF* mutation status, and AJCC (v8) M stage. The primary endpoint was progression-free survival (PFS) per RECIST v1.1 as assessed by blinded independent central review. Secondary endpoints were overall survival and objective response rate. PFS in prespecified subgroups and safety were additional objectives. **Results:** 714 patients were randomized to RELA+NIVO FDC (n = 355) or NIVO (n = 359). Patient characteristics were well balanced between treatment groups. Median follow-up was 13.2 months. Median PFS in the RELA+NIVO FDC group (10.1 months [95% CI, 6.4–15.7]) was significantly longer than in the NIVO group (4.6 months [95% CI, 3.4–5.6]; hazard ratio, 0.75 [95% CI, 0.6–0.9]; $P = 0.0055$). PFS rates at 12 months were 47.7% (95% CI, 41.8–53.2) and 36.0% (95% CI, 30.5–41.6) for RELA+NIVO FDC and NIVO, respectively. PFS favored RELA+NIVO FDC across key prespecified subgroups. The incidence of grade 3/4 treatment-related adverse events (TRAEs) was higher in the RELA+NIVO FDC group (18.9%) versus NIVO (9.7%). There were 3 treatment-related deaths with RELA+NIVO FDC and 2 with NIVO. TRAEs (any grade) led to treatment discontinuation in 14.6% and 6.7% of patients in the RELA+NIVO FDC and NIVO groups, respectively. **Conclusions:** First-line treatment with RELA+NIVO FDC demonstrated a statistically significant PFS benefit compared to NIVO monotherapy in patients with advanced melanoma. RELA+NIVO FDC was well tolerated with a manageable safety profile and without unexpected safety signals. This is the first phase III study of a novel FDC to demonstrate a clinically meaningful benefit by dual inhibition of the LAG-3 and PD-1 pathways. Clinical trial information: NCT03470922. Research Sponsor: Bristol-Myers Squibb.

Lenvatinib (len) plus pembrolizumab (pembro) for patients (pts) with advanced melanoma and confirmed progression on a PD-1 or PD-L1 inhibitor: Updated findings of LEAP-004.

Ana Maria Arance, Luis de la Cruz-Merino, Teresa M. Petrella, Rahima Jamal, Lars Ny, Ana Carneiro, Alfonso Berrocal, Ivan Marquez-Rodas, Anna Spreafico, Victoria Atkinson, Fernanda Costa Svedman, Andrew Mant, Alan D. Smith, Ke Chen, Scott J. Diede, Clemens Krepler, Georgina V. Long; Hospital Clinic Barcelona, Barcelona, Spain; Hospital Universitario Virgen Macarena, Seville, Spain; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Centre hospitalier de l'Université de Montréal, Montréal, ON, Canada; University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden; Skåne University Hospital and Lund University, Lund, Sweden; Hospital General Universitario de Valencia, Valencia, Spain; Hospital General Universitario Gregorio Marañón and CIBERONC, Madrid, Spain; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Alexandra Hospital, University of Queensland, Brisbane, Australia; Karolinska University Hospital, Stockholm, Sweden; Eastern Health, Monash University, Melbourne, Australia; Eisai Ltd., Hatfield, United Kingdom; Merck & Co., Inc., Kenilworth, NJ; Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Background: Initial results of the open-label, single-arm, phase 2 LEAP-004 study (NCT03776136) showed that len and pembro in combination had promising efficacy and manageable safety in pts with unresectable stage III-IV melanoma and confirmed PD on a PD-(L)1 inhibitor given alone or in combination. ORR was 21.4% with a 6.3-mo median DOR; ORR was 31.0% in patients with PD on prior anti–PD-1 + anti–CTLA-4. We present updated data from LEAP-004 and additional ORR subgroup analyses. **Methods:** Eligible pts with PD confirmed per iRECIST within 12 wk of the last dose of a PD-(L)1 inhibitor given alone or with anti–CTLA-4 or other therapies for $\geq$2 doses received len 20 mg/d once daily plus $\leq$35 doses of pembro 200 mg Q3W until PD or unacceptable toxicity. Primary end point is ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points are PFS and DOR per RECIST v1.1 by BICR, OS, and safety. ORR was calculated for pts with PD on prior anti–PD-1 + anti–CTLA-4, pts whose only prior anti–PD-(L)1 was in the adjuvant setting, pts with primary resistance (ie, best response of SD or PD to prior anti–PD-(L)1 in the advanced setting) and pts with secondary resistance (ie, PD following best response of CR or PR on prior anti–PD-(L)1 in the advanced setting). **Results:** 103 pts were enrolled. Median age was 63 y, 68.0% of pts had stage M1c/M1d disease, 55.3% had LDH $>$ ULN (20.4% $\geq$2 $\times$ ULN), 58.3% received $\geq$2 prior treatments, 94.2% received therapy for advanced disease, and 32.0% received BRAF ± MEK inhibition. With median study follow-up of 15.3 mo (range 12.1-19.0), 17.5% of pts were still receiving study drug. ORR by BICR remained 21.4% (95% CI 13.9-30.5), although the number of CRs increased from 2 to 3. DCR was 66.0%. Median DOR increased to 8.2 mo, and the KM estimate of DOR $\geq$9 mo was 37.2%. ORR was 33.3% in pts with PD on prior anti–PD-1 + anti–CTLA-4 (n = 30), 18.2% in pts whose only prior anti–PD-1/L1 was in the adjuvant setting (n = 11), 22.6% in pts with primary resistance (n = 62), and 22.7% in pts with secondary resistance (n = 22). Median (95% CI) PFS and OS in the total population were 4.2 mo (3.8-7.1) and 14.0 mo (95% CI 10.8-NR); 12-mo PFS and OS estimates were 17.8% and 54.5%. Incidence of treatment-related AEs was as follows: 96.1% any grade, 45.6% grade 3-4, 1.0% grade 5 (decreased platelet count), 7.8% led to discontinuation of len and/or pembro, and 56.3% led to len dose reduction. **Conclusions:** The combination of len and pembro continues to show clinically meaningful, durable responses in pts with advanced MEL with confirmed progression on a prior PD-(L)1 inhibitor, including those with PD on anti–PD-1 + anti–CTLA-4 therapy, and regardless of primary or secondary resistance to prior anti–PD-(L)1 therapy. The safety profile was consistent with prior studies of len + pembro. These data support len + pembro as a potential regimen for this population of high unmet need. Clinical trial information: NCT03776136. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Lifileucel (LN-144), a cryopreserved autologous tumor infiltrating lymphocyte (TIL) therapy in patients with advanced melanoma: Evaluation of impact of prior anti-PD-1 therapy.

James Larkin, Amod Sarnaik, Jason Alan Chesney, Nikhil I. Khushalani, John M. Kirkwood, Jeffrey S. Weber, Karl D. Lewis, Theresa Michelle Medina, Harriet M. Kluger, Sajeve Samuel Thomas, Evidio Domingo-Musibay, Judit Olah, Eric D. Whitman, Salvador Martin-Algarra, Philippa Gail Corrie, Jose Lutzky, Wen Shi, Renee Xiao Wu, Maria Fardis, Omid Hamid; Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; H. Lee Moffitt Cancer Center, Tampa, FL; Brown Cancer Center, University of Louisville, Louisville, KY; Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center, Tampa, FL; University of Pittsburgh Medical Center, Pittsburgh, PA; Laura and Isaac Perlmutter Cancer Center, NYU Langone, New York, NY; University of Colorado Comprehensive Cancer Center, Aurora, CO; Yale School of Medicine and Smilow Cancer Center, Yale New Haven Hospital, New Haven, CT; University of Florida-Health Cancer Center, Orlando Health, Orlando, FL; University of Minnesota, Masonic Cancer Center, Minneapolis, MN; University of Szeged Szent-Györgyi Medical University, Szeged, Hungary; Atlantic Health System Cancer Care, Morristown, NJ; Clinica Universidad de Navarra, Pamplona, Spain; Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Mount Sinai Medical Center, Miami Beach, FL; Iovance Biotherapeutics, Inc., San Carlos, CA; The Angeles Clinic and Research Institute, Los Angeles, CA

Background: Immune checkpoint inhibitors (ICI) have become standard of care for treatment of metastatic melanoma. Most patients with advanced melanoma progress on ICI and treatment options are limited for these patients. Progression may be through primary resistance (lack of response) or secondary resistance (initial response then progression). Lifileucel is an adoptive cell therapy using TIL, that has shown efficacy in patients with advanced melanoma who progress on/after an anti-PD-1 (Sarnaik, 2020). We present the 28-month (mos) follow-up data and highlight the impact of prior anti-PD-1 response and duration of exposure on outcome with lifileucel. **Methods:** C-144-01 is a Phase 2, open-label, multicenter study of efficacy and safety of lifileucel in patients with advanced melanoma who have progressed on anti-PD-1 therapy and BRAFi ± MEKi, if BRAF V600^{+}. We report long-term follow up on Cohort 2 (N = 66). Tumors were resected at local sites, processed in central GMP facilities for TIL production in a 22-day manufacturing process. Therapy consisted of nonmyeloablative lymphodepletion using 2 days of cyclophosphamide and 5 days of fludarabine, a single infusion of lifileucel, and up to six doses of IL-2. Objective response rate (ORR) was assessed by RECIST 1.1. Data cutoff was Dec. 14, 2020. **Results:** Baseline characteristics: 3.3 mean prior therapies (100% anti-PD-1; 80% anti-CTLA-4; 23% BRAFi/MEKi), high baseline tumor burden (106 mm mean target lesion SOD), 42% liver/brain lesions, 40.9% LDH $>$ ULN. ORR by investigator was 36.4% (3 CR, one new CR developed at 24 mos; 21 PR). Median duration of response (mDOR) was not reached at median follow-up of 28 mos (DOR range: 2.2- 35.2 mos). In responders, the median cumulative duration and median prior lines of anti-PD-1 therapy was 4.4 mos (range: 1.4-22.5 mos), and 1.5 (range: 1-4). Data in Table demonstrates a meaningful increase in DOR to TIL with primary anti-PD-1 resistance and lower duration of time on prior anti-PD-1 therapy. No new safety risks have been identified for lifileucel during long-term follow-up. **Conclusions:** One-time lifileucel treatment results in a 36.4% ORR, and mDOR was not reached at 28 mos of median study follow up. One PR converted to a new CR at 24 months as responses continue to deepen. DOR is positively associated with primary resistance to prior anti-PD-1 therapy and with shorter cumulative prior duration of anti-PD-1 therapy. Lifileucel may offer a better clinical outcome when used earlier upon detection of progression on prior anti-PD-1 rather than retreatment with anti-PD-1 based regimens. Clinical trial information: NCT02360579. Research Sponsor: Iovance Biotherapeutics, Inc.

Univariate Cox-regression analyses on DOR.

	Cohort 2 Responders (N=24)	
	HR (95% CI)	nominal p value
Primary refractory to anti-PD-1/PD-L1 (Y vs N)	0.263 (0.075, 0.921)	0.0367
Duration of prior anti-PD-1/PD-L1 use (≤ median of 5.1 mos vs > median)	0.218 (0.056, 0.854)	0.0288

CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma.

Jedd D. Wolchok, Vanna Chiarion-Sileni, Rene Gonzalez, Jean-Jacques Grob, Piotr Rutkowski, Christopher D. Lao, Charles Lance Cowey, Dirk Schadendorf, John Wagstaff, Reinhard Dummer, Pier Francesco Ferrucci, Michael Smylie, Marcus O. Butler, Andrew Graham Hill, Ivan Marquez-Rodas, John B. A. G. Haanen, Tuba Bas, Wim van Dijck, James Larkin, F. Stephen Hodi; Medical Oncology, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, NY; Oncology Institute of Veneto IRCCS, Padua, Italy; University of Colorado Cancer Center, Denver, CO; Aix-Marseille University, APHM, Hôpital Timone, Marseille, France; Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland; Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Department of Dermatology, University of Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; The College of Medicine, Swansea University, Swansea, United Kingdom; Skin Cancer Center, University Hospital of Zürich, Zürich, Switzerland; European Institute of Oncology–IRCCS, Milan, Italy; Cross Cancer Institute, Edmonton, AB, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Tasman Oncology Research, Southport, QLD, Australia; Medical Oncology, General University Hospital Gregorio Marañón & CIBERONC, Madrid, Spain; Netherlands Cancer Institute, Amsterdam, Netherlands; Bristol Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Princeton, NJ; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Dana-Farber Cancer Institute, Boston, MA

Background: In the phase 3 CheckMate 067 trial, a durable and sustained clinical benefit was achieved with nivolumab (NIVO) + ipilimumab (IPI) and NIVO alone vs IPI at 5-y of follow-up (overall survival [OS] and progression-free survival [PFS] rates: 52%, 44%, 26% and 36%, 29%, 8%, respectively). Here we report 6.5-y efficacy and safety outcomes. **Methods:** Eligible pts with previously untreated unresectable stage III or IV melanoma were randomly assigned in a 1:1:1 ratio and stratified by PD-L1 status, *BRAF* mutation status, and metastasis stage. Pts received NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W followed by NIVO 3 mg/kg Q2W (n = 314), NIVO 3 mg/kg Q2W + placebo (n = 316), or IPI 3 mg/kg Q3W for 4 doses + placebo (n = 315) until progression or unacceptable toxicity. Co-primary endpoints were PFS and OS with NIVO + IPI or NIVO vs IPI. Secondary endpoints included objective response rate (ORR), descriptive efficacy assessments of NIVO + IPI vs NIVO alone, and safety. **Results:** With a minimum follow-up of 6.5 y, median OS was 72.1 mo with NIVO + IPI, 36.9 mo with NIVO, and 19.9 mo with IPI (table). Median time from randomization to subsequent systemic therapy was not reached (NR; 95% CI, 59.6–NR) with NIVO + IPI, 25.2 mo (95% CI, 16.0–43.2) with NIVO, and 8.0 mo (95% CI, 6.5–8.7) with IPI; 36%, 49%, and 66% of pts, respectively, received any subsequent systemic therapy. Median treatment-free interval (which excluded pts who discontinued follow-up prior to initiation of subsequent systemic therapy) was 27.6 mo (range, 0–83.0), 2.3 mo (range, 0.2–81.6), and 1.9 mo (range, 0.1–81.9) with NIVO + IPI, NIVO, and IPI, respectively. Of the pts alive and in follow-up, 112/138 (81%; NIVO + IPI), 84/114 (74%; NIVO), and 27/63 (43%; IPI) were off treatment and never received subsequent systemic therapy; 7, 8, and 0 pts, respectively, were still on treatment. Grade 3/4 treatment-related adverse events were reported in 59% of NIVO + IPI-treated pts, 24% of NIVO-treated pts, and 28% of IPI-treated pts. Since the 5-y analysis, no new safety signals were observed and no additional treatment-related deaths occurred. **Conclusions:** This 6.5-y analysis represents the longest follow-up from a phase 3 melanoma trial in the modern checkpoint inhibitor combination therapy and targeted therapy era. The results show durable improved outcomes with NIVO + IPI and NIVO vs IPI in pts with advanced melanoma. We observed improvement in OS, PFS, and ORR with NIVO + IPI over NIVO alone. Clinical trial information: NCT01844505. Research Sponsor: Bristol Myers Squibb.

	NIVO + IPI(N = 314)	NIVO (N = 316)	IPI (N = 315)
Median OS: all pts, mo (95% CI)	72.1(38.2–NR)	36.9(28.2–NR)	19.9(16.8–24.6)
6.5-y OS rate: all pts, % (95% CI)	49(44–55)	42(37–42)	23(19–28)
BRAF mutant	57(47–66)	43(33–53)	25(17–34)
Median PFS: all pts, mo (95% CI)	11.5(8.7–19.3)	6.9(5.1–10.2)	2.9(2.8–3.2)
6.5-y PFS rate: all pts, % (95% CI)	34(29–40)	29(23–34)	7(4–11)
Investigator-assessed ORR, % (95% CI)	58.3(52.6–63.8)	44.9(39.4–50.6)	19.0(14.9–23.8)
Duration of response, mo (95% CI)	NR(61.9–NR)	NR(45.7–NR)	19.3(8.8–47.4)

9507 **Oral Abstract Session**

Five-year overall survival (OS) in COLUMBUS: A randomized phase 3 trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients (pts) with *BRAF* V600-mutant melanoma.

Reinhard Dummer, Keith Flaherty, Caroline Robert, Ana Maria Arance, Jan Willem de Groot, Claus Garbe, Helen Gogas, Ralf Gutzmer, Ivana Krajsová, Gabriella Liszkay, Carmen Loquai, Mario Mandalà, Dirk Schadendorf, Naoya Yamazaki, Michael D. Pickard, Fabian Zohren, Michelle L. Edwards, Paolo Antonio Ascierto; University Hospital Zürich, Zurich, Switzerland; Massachusetts General Hospital, Boston, MA; Institut Gustave Roussy, Villejuif, France; Hospital Clinic of Barcelona, Barcelona, Spain; Isala Oncology Center, Zwolle, Netherlands; University Hospital Tübingen, Tübingen, Germany; National and Kapodistrian University of Athens, Athens, Greece; Hannover Medical School, Hannover, Germany; University Hospital Prague, Prague, Czech Republic; National Institute of Oncology, Budapest, Hungary; University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; University of Perugia, Perugia, Italy; West German Cancer Center, Essen, Germany; National Cancer Center Hospital, Tokyo, Japan; Pfizer, Boulder, CO; Pfizer, La Jolla, CA; Pfizer, New York, NY; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy

Background: Combined BRAF/MEK inhibitor therapy has demonstrated benefits on progression-free survival (PFS) and OS and is standard of care for the treatment of advanced *BRAF* V600-mutant melanoma. Here we report a 5-year update from the COLUMBUS trial. **Methods:** In Part 1 of COLUMBUS, 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 (COMBO450), encorafenib 300 mg QD (ENCO300), or vemurafenib 960 mg BID (VEM). An updated analysis including PFS, OS, objective response rate (ORR; by blinded independent central review), and safety was conducted after minimum follow-up of 65.2 months (mo). Data are as is; study is ongoing. **Results:** At data cut-off (Sep 15, 2020), there were 131 (68%), 117 (60%), and 145 (76%) deaths in the COMBO450, ENCO300, and VEM treatment arms, respectively. The median OS (95% CI) and 5-year OS rate (95% CI) with COMBO450 were 33.6 (24.4–39.2) mo and 34.7% (28.0–41.5), respectively (median follow-up: 70.4 mo). The 5-year OS rate (95% CI) in COMBO450 pts who had normal lactate dehydrogenase (LDH) levels at baseline was 45.1% (36.5–53.2). Median OS and 5-year OS rates for ENCO300 and VEM, as well as for pts with normal and high LDH levels and $>$ 3 organs involved at baseline, are shown in the table. For COMBO450, ENCO300, and VEM, the 5-year PFS rate was 22.9%, 19.3%, and 10.2%; ORR (95% CI) was 64.1% (56.8–70.8), 51.5% (44.3–58.8), and 40.8% (33.8–48.2); and the median duration of response (DOR) was 18.6, 15.5, and 12.3 mo, respectively. Safety results were consistent with the known tolerability profile of COMBO450. Additional efficacy and updated safety analyses will be presented. Following study drug discontinuation, the most common subsequent treatment in all arms was checkpoint inhibitors. **Conclusions:** Updated OS and DOR results with COMBO450 demonstrate continued long-term benefits in pts with *BRAF* V600-mutant melanoma. Clinical trial information: NCT01909453. Research Sponsor: Pfizer.

	COMBO450			ENCO300			VEM		
	Events/ pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/ pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/ pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)
All pts	131/ 192 (68.2)	33.6 (24.4–39.2)	34.7% (28.0–41.5)	117/ 194 (60.3)	23.5 (19.6–33.6)	34.9% (27.9–42.0)	145/ 191 (75.9)	16.9 (14.0–24.5)	21.4% (15.7–27.8)
LDH normal	81/ 137 (59.1)	51.7 (36.8–67.3)	45.1% (36.5–53.2)	79/ 147 (53.7)	35.3 (23.7–60.5)	41.8% (33.3–50.1)	95/ 139 (68.3)	24.5 (18.6–29.1)	28.4% (20.9–36.4)
LDH high	50/55 (90.9)	11.4 (9.0–17.4)	9.1% (3.3–18.4)	38/47 (80.9)	9.2 (7.0–16.2)	13.8% (5.6–25.6)	50/52 (96.2)	9.6 (8.5–11.5)	4.0% (0.7–12.1)
> 3 organs involved	35/42 (83.3)	11.6 (9.1–20.8)	–	32/44 (72.7)	15.7 (7.9–19.7)	–	39/45 (86.7)	10.9 (8.6–15.7)	–

*Unstratified Cox regression model.

9508 **Oral Abstract Session**

Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): Randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets).

Georgina V. Long, Victoria Atkinson, Serigne Lo, Alexander David Guminski, Shahneen Kaur Sandhu, Michael Paul Brown, Maria Gonzalez, Richard A. Scolyer, Louise Emmett, Grant A. McArthur, Alexander M. Menzies; Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; Princess Alexandra Hospital, University of Queensland, Greenslopes, Brisbane, QLD, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Royal North Shore Hospital, Sydney, Australia; Peter MacCallum Cancer Center, Melbourne, VIC, Australia; Royal Adelaide Hospital, Adelaide, Australia; Melanoma Institute Australia, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, Australia; St Vincent's Clinic Medical Imaging and Nuclear Medicine, Darlinghurst, Australia; Melanoma and Skin Service and Cancer Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Background: Preliminary data from the ABC (76 pts) and CheckMate 204 (94 pts) trials showed that nivo and nivo+ipi have activity in active melanoma brain metastases, with durable responses in a subset of pts. Here, we report updated 5-yr data from all pts enrolled on the ABC trial (NCT02374242). **Methods:** This open-label ph2 trial enrolled 3 cohorts of pts with active melanoma brain mets naïve to anti-PD1/PDL1/PDL2/CTLA4 from Nov 2014-Apr 2017. Pts with asymptomatic brain mets with no prior local brain therapy were randomised to cohort A (nivo 1mg/kg + ipi 3mg/kg, Q3Wx4, then nivo 3mg/kg Q2W) or cohort B (nivo 3mg/kg Q2W). Cohort C (nivo 3mg/kg Q2W) had brain mets i) that failed local therapy, ii) with neuro symptoms and/or iii) with leptomeningeal disease. Prior BRAF inhibitor (BRAFi) was allowed. The primary endpoint was best intracranial response (ICR) ≥wk12. Key secondary endpoints were IC PFS, overall PFS, OS, & safety. **Results:** A total of 76 pts (med f/u 54 mo) were enrolled; median age 59y, 78% male. For cohorts A, B and C: elevated LDH 51%, 58% and 19%; V600BRAF 54%, 56% and 81%; prior BRAFi 23%, 24%, 75%. Efficacy and toxicity are shown in the table. There were no treatment-related deaths. 1/17 deaths in cohort A & 4/16 in cohort B were due to IC progression only. **Conclusions:** Nivo monotherapy and ipi+nivo are active in melanoma brain mets, with durable responses in the majority of patients who received ipi+nivo upfront. A study of upfront ipi+nivo+/-SRS is underway (NCT03340129).Clinical trial information: NCT02374242. Research Sponsor: BMS, Other Foundation.

	A (ipi+nivo)	B (nivo)	C (nivo)
All patients	n=35	n=25	n=16
ICR	51%	20%	6%
5-yr IC PFS	46%	15%	6%
5-yr OS	51%	34%	13%
Rx naïve	n=27	n=19	n=4
ICR (Rx naïve)	59%	21%	25%
5-yr IC PFS (Rx naïve)	52%	14%	.
5-yr OS (Rx naïve)	55%	40%	25%
TRAE G3/4	63%	20%	13%

9509 **Clinical Science Symposium**

Overall survival benefit from tebentafusp in patients with best response of progressive disease.

Anthony M. Joshua, Jean-Francois Baurain, Sophie Piperno-Neumann, Paul Nathan, Jessica Cecile Hassel, Marcus O. Butler, Max Schlaak, Ryan Sullivan, Sebastian Ochsenreither, Reinhard Dummer, John M. Kirkwood, Joseph J. Sacco, Alexander Noor Shoushtari, Marlana Orloff, Josep M. Piulats, Shaad Essa Abdullah, Mughda Deo, Sarah Lockwood, Piotr Rutkowski; Kinghorn Cancer Centre, St Vincent's Hospital, Darlinghurst, NSW, Australia; Institut Roi Albert II Cliniques Universitaires St-Luc, Brussels, Belgium; Institut Curie, Paris, France; Mount Vernon Cancer Centre, London, United Kingdom; Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; University Hospital, Department of Dermatology and Allergy, LMU Munich, Munich, Germany; Massachusetts General Hospital, Boston, MA; Charité Comprehensive Cancer Center, Berlin, Germany; Skin Cancer Center, University Hospital of Zürich, Zürich, Switzerland; University of Pittsburgh Medical Center, Pittsburgh, PA; Clatterbridge Cancer Centre, Merseyside, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA; Instituto Català de Oncologia, Hospital Duran i Reynals, L'Hospitalet de Llobregat, Hospitalet De Llobregat, Spain; Immunocore, Abingdon, United Kingdom; Pivotal Statistics Ltd, Macclesfield, United Kingdom; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Background: Tebentafusp (tebe) is the first T cell receptor (TCR) therapeutic to demonstrate an overall survival (OS) benefit in a randomized Phase 3 (Ph3) study [NCT03070392]. In Ph2, 42% of pts with best overall response (BOR) of progressive disease (PD) survived $>$ 1 year (yr), suggesting RECIST-based radiographic assessments underestimate OS benefit of tebe. Here we analyzed OS in the Ph3 study in a cohort of pts with BOR of PD by comparing tebe to the control arm of investigator's choice (IC). **Methods:** 378 pts were randomized in a 2:1 ratio to tebe vs. IC. BOR was assessed by investigators using RECIST v1.1. Treatment beyond first disease progression (TBP) was permitted for both arms. On the IC arm, only patients receiving pembrolizumab (pembro) continued with TBP and were included in the TBP-related analyses. No crossover to tebe was permitted; investigators were free to choose subsequent therapy. This analysis was conducted on the first interim analysis (data extracted Nov-2020). Kaplan-Meier estimates of OS were based on Day 100 landmark to eliminate immortal time bias and to capture majority of the PDs. **Results:** By Day 100, PD as BOR occurred in 52% (130/252) of tebe pts (PD-tebe) vs. 60% (76/126) of IC pts (PD-IC). Key baseline characteristics including lactate dehydrogenase, alkaline phosphatase, ECOG performance, age, and sex were similar between PD-tebe vs PD-IC. The proportion of pts with PD due to progression of target lesions (TL), non-TL, or new lesions were also similar between the two groups. More pts received TBP among PD-tebe 53% (69/130) vs PD-pembro 16% (10/61). Median duration of TBP was longer for PD-tebe (7 weeks) vs PD-Pembro (3 weeks). The safety profile of PD-tebe pts during TBP was similar to all tebe-treated pts. OS was superior for PD-tebe vs PD-IC, HR = 0.41 (95%CI 0.25-0.66), even when considering key baseline covariates. While some pts had regression of TL despite diagnosis of PD ($<$ 10% of pts), the OS benefit remained even when limited to pts with best change of tumor growth of TL, HR 0.46 (0.29, 0.73). 58% (75/130) PD-tebe and 52% (40/76) PD-IC pts received subsequent therapies. In a landmark OS analysis of these pts beginning on 1st day of subsequent therapy, prior tebe was associated with better OS vs. prior IC, HR 0.59 (95%CI 0.36-0.96). **Conclusions:** Tebe is the first TCR therapeutic to demonstrate an OS benefit in a solid tumor. Surprisingly, a strong OS benefit from tebe is observed even in pts with BOR of PD, suggesting that RECIST-based radiographic assessments do not capture the complete benefit from tebe. The safety profile of tebe during TBP was consistent with that for long-term tebe treatment. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9510 **Clinical Science Symposium**

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

Jonathan S. Zager, Marlana Orloff, Pier Francesco Ferrucci, Evan Scott Glazer, Aslam Ejaz, Erika Richtig, Sebastian Ochsenreither, Michael C. Lowe, Sunil A. Reddy, Georgia Beasley, Anja Gesierich, Reinhard Dummer, Ana Maria Arance, Stephen William Fenwick, Matthew Wheater, Christian Ottensmeier; H. Lee Moffitt Cancer Ctr, Tampa, FL; Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA; European Institute of Oncology–IRCCS, Milan, Italy; University of Tennessee Health Science Center, Memphis, TN; Division of Surgical Oncology, Department of Surgery, The Ohio State University, Columbus, OH; Medical University of Graz, Graz, Austria; Department of Hematology, Oncology, and Tumor Immunology, Charité Campus Benjamin Franklin, Berlin, Germany; Emory University School of Medicine, Atlanta, GA; Stanford Cancer Institute, Stanford, CA; Duke University, Durham, NC; University Hospital Wuerzburg, Würzburg, Germany; Skin Cancer Center, University Hospital of Zürich, Zürich, Switzerland; Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom; University Hospital Southampton, Southampton, United Kingdom; The Clatterbridge Cancer Center NHS Foundation Trust, Liverpool, United Kingdom

Background: Ocular melanoma, the most common intraocular malignancy, frequently metastasizes to the liver but to date there is no established standard of care for hepatic-dominant ocular melanoma patients. The FOCUS trial began as a randomized, phase III trial (301) comparing PHP with best alternative care (BAC). The trial was subsequently amended (301A) to remove the BAC arm due to enrollment concerns. **Methods:** Eligible patients with hepatic-dominant ocular melanoma were randomized 1:1 to receive PHP or BAC (investigator's choice of TACE, pembrolizumab, ipilimumab, or dacarbazine) on the 301 trial. All eligible patients received PHP on the 301A trial. PHP patients could receive up to 6 PHP treatments, repeated every 6-8 weeks with melphalan dosed at 3.0mg/kg ideal body weight (IBW). Patients with progressive disease (PD) were discontinued from study treatment and all patients are followed until death. Patientswere imaged every 12 (±2) weeks until PD. The primary endpoint, ORR (per RECIST 1.1) as assessed by Independent Review Committee, will be characterized by the point estimate and 95% CI for each group (PHP and BAC). Categorical efficacy variables will be presented as frequency counts and percentages and 95% CI. Time-to-event variables will be summarized using Kaplan-Meier methods (median and 95% CI). **Results:** 144 patients were enrolled overall; 102 were assigned to PHP (301: n=43; 301A: n=59) and 42 were assigned to BAC. 91 PHP patients received treatment (301: n=40; 301A: n=51) and 32 BAC patients received treatment. At the time of this analysis, 4 PHP patients were still ongoing on study treatment with a minimum follow-up of 24 weeks. 79 PHP-treated patients and 29 BAC-treated patients were evaluable for response. ORR among PHP patients was 32.9% (26/79; 95% CI: 22.75-40.40%). ORR among BAC patients was 13.8% (4/29; 95% CI: 3.89-31.66%). The median PFS was 9.03 months (95% CI: 6.24-11.83) among PHP patients and was 3.06 months (95% CI: 2.69-5.65) among BAC patients; this difference was statistically significant (p=0.0004). Among the 94 patients assessed for safety after treatment with PHP, 40.4% of patients experienced a serious treatment-emergent adverse event, the majority of which were hematological and resolved without sequelae. There were no treatment related deaths in the trial. **Conclusions:** In this analysis of preliminary data from the FOCUS trial, PHP demonstrates a statistically superior ORR and significantly prolonged PFS in comparison with BAC in the treatment of hepatic metastases from ocular melanoma. The data is encouraging as efficacious treatments for hepatic metastases from ocular melanoma are desperately needed. These early data show an improvement over the previous phase III study in terms of both efficacy (ORR and PFS) as well as toxicity using second generation filters. Clinical trial information: NCT02678572. Research Sponsor: Delcath Systems, Inc.

9511 **Clinical Science Symposium**

Atezolizumab in combination with bevacizumab in patients with unresectable locally advanced or metastatic mucosal melanoma: Interim analysis of an open-label phase II trial.

Lu Si, Meiyu Fang, Yu Chen, Lili Mao, Peng Zhang, Jing Lin, Xue Bai, Xiao Cao, Yi Chen, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, China; Department of Medical Oncology, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital, Fuzhou, China; Department of Rare Cancer & Head and Neck Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences; Key Laboratory of Head & Neck Cancer Translational Research of Zhejiang Province, Hangzhou, China; Shanghai Roche Pharmaceuticals Ltd., Shanghai, China

Background: Mucosal melanoma is a rare malignant melanoma in Caucasians but ranks the second most common subtype in the Asian population. It is more often diagnosed at an advanced stage and responds poorly to current PD-1/PD-L1 inhibitors. Here we report the interim analysis results of ML41186, an open-label, multicenter, single-arm phase II study, aiming to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab in patients (pts) with advanced mucosal melanoma. **Methods:** Eligible pts aged 18 to 75 years with histologically confirmed unresectable locally advanced or metastatic mucosal melanoma had at least one measurable lesion per RECIST version 1.1 at baseline, with an ECOG PS 0 or 1 and adequate hematologic and organ function. ML41186 is a Simon two-stage design study, if 22 pts completed ORR evaluation and more than 3 pts respond in stage I, the study then continue to Stage II. Atezolizumab and bevacizumab were administered at a fixed dose of 1200 mg and 7.5 mg/kg Q3W respectively (on day 1 of each 21-day cycle) until unacceptable toxicity or loss of clinical benefit. The primary endpoint is the objective response rate (ORR). The secondary endpoints include progression-free survival (PFS), duration of objective response (DoR), disease control rate (DCR), and safety. **Results:** By the cut-off date of 9th September 2020, 35 pts has been enrolled, among whom 22 pts in the stage I analysis set has completed two efficacy evaluation, while 28 pts (full analysis set) has completed at least one efficacy evaluation. In ITT populations (n=35), mean age was 58.9 years with 10 (28%) pts had ECOG PS of 1. LDH level elevated in 9 (25.7%) pts. More than half pts (19, 54.3%) had metastatic mucosal melanoma, of whom 3 (15.8%) pts had more than 3 metastasis sites and 4 (21.1%) pts had liver metastasis. In stage I analysis set (n=22), the best confirmed ORR was 36.4% (95% CI, 17.0%-59.3%). Median progression-free survival was 5.32 months (95% CI, 1.58-not reached), and the best confirmed DCR was 59.1% (95%CI, 36.4%-79.3%). The median confirmed DoR was not reached (95% CI, 2.76-NR). In the full analysis set (n=28), the unconfirmed ORR was 42.9% (95%CI, 24.5%-62.8%). In ITT populations (n=35), 28 pts (80%) experienced at least one adverse event (AE) and 5 pts (14.3%) experienced at least one grade 3-4 AEs. Only one patient experienced AE leading to treatment discontinuation. One patient died of autoimmune lung disease. **Conclusions:** The combination of atezolizumab plus bevacizumab showed promising benefit and was tolerable in pts with advanced mucosal melanoma. At the time of this interim analysis, the primary endpoint did not cross the futility boundary, thus the study will run into Stage II. Clinical trial information: NCT04091217. Research Sponsor: Shanghai Roche Pharmaceuticals Ltd., Shanghai, China.

9512 **Clinical Science Symposium**

A phase 2 clinical trial of neoadjuvant anti-PD-1 ab (Toripalimab) plus axitinib in resectable mucosal melanoma.

Chuanliang Cui, Xuan Wang, Bin Lian, Lu Si, Zhihong Chi, Xinan Sheng, Yan Kong, Lili Mao, Xue Bai, Bixia Tang, Xieqiao Yan, Siming Li, Li Zhou, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: The outcome of patients (pts) with resectable mucosal melanoma (MM) is still poor. Toripalimab combined with axitinib has shown impressive results in metastatic MM with an ORR of 48.3% and a median PFS of 7.5 months in a phase 1b trial. It was hypothesized that this combination therapy might cause pathologic response in neoadjuvant setting for resectable MM, so we conducted this single arm phase 2 trial. **Methods:** Eligible pts were adults (aged 18 to 75) with histologically confirmed resectable (localized or regional lymph node metastasis) MM disease. Exclusion criteria included ocular or unknown primary melanoma, distant metastatic disease or previous use of anti PD-1 ab. Pts received toripalimab 3 mg/kg Q2W plus axitinib 5 mg BID for 8 weeks as neoadjuvant therapy, then surgery and the adjuvant toripalimab 3 mg/kg Q2W starting 2±1week after surgery for totally 52 weeks. The primary end point is pathologic response rate according to the International Neoadjuvant Melanoma Consortium (pCR+pPR, pCR is defined as the complete absence of residual viable tumor and pPR $\leq$ 50% of viable tumor cells). The secondary end point is RFS in the ITT population. Clinical trial information: NCT04180995. **Results:** From Aug 2019 to Dec 2020, 21 pts have been eligible and enrolled. Basic characteristics: median age 62 years; M: F 28.6% : 71.4%; primary sites 8 femal genital(1urethra, 7vagina), 5 esophagus, 4 ano-rectal, 4 head & neck(3 nasal,1 oral), in which 47.6% localized disease (T3/4 60%), 52.4% regional lymphatic disease; Gene mutation: 4 cKit (1 amplification), 2 Nras,1 Braf (N581), 1mTOR. This therapy was tolerable with grade 3-4 treatment related AEs of 23.8% (liver dysfunction 14.3%, hyperglycemia 9.5% and hypertension 4.8%). 13 pts had received surgeries (local excision 30.8%, wide excision ± CLND72.7%)and 5 pts still in neoadjuvant treatment. One patient was inoperable for bone metastasis, and 2 pts withdrew for covid 19 epidemic. At a median follow up time of 59 weeks, the pathologic response rate was 28.6% (4/14, 2 pCR, 2pPR). Of the post-surgical specimens, 61.5% (8/13) showed significant TIL infiltration, with 38.5% Brisk and 23.1% Nonbrisk according to the definition of AJCC 8th edition. Plenty of plasma cells, histiocyte and pigment with hyaline fibrosis were also found in responders. No recurrence or metastasis was observed in responders until now, with a RFS reaching more than 58weeks. 5 pts with pNR($>$ 50% viable tumor cells) got disease progression, with 1 local recurrence, 1 regional lymphatic metastasis, and 3 distant metastases. The median RFS has not been reached. **Conclusions:** Neoadjuvant toripalimab plus axitinib in resectable MM has shown promising pathologic responses with good tolerance, which supports further investigation of neoadjuvant therapies in MM. Survival is still in follow-up. Clinical trial information: NCT04180995. Research Sponsor: Shanghai Junshi biosciences Co.

9514 **Poster Discussion Session**

Phase II study of ceralasertib (AZD6738), in combination with durvalumab in patients with metastatic melanoma who have failed prior anti-PD-1 therapy.

Minsuk Kwon, Seung Tae Kim, Simon Smith, Claire Smith, Peter G. Mortimer, Bienvenu LoembE, Iwanka Kozarewa, Emma Dean, Jeeyun Lee; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Early Oncology Clinical Science, R&D Oncology, AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Cambridge, United Kingdom

Background: Alterations in DNA damage response (DDR) and repair are associated with genomic instability and increased somatic tumor mutational burden, and modulating DNA repair is a promising strategy to boost the efficacy of cancer immunotherapy. Ceralasertib is an oral inhibitor of the serine/threonine protein kinase Ataxia Telangiectasia and Rad3 Related (ATR), which is crucial to the cell's response to replication stress. **Methods:** This phase 2 trial was designed to evaluate the efficacy and safety of ceralasertib in combination with durvalumab in patients with metastatic melanoma (MM) who had failed to anti-PD-1 therapy. The study drug schedule was: ceralasertib at 240 mg BD on days 15 to 28 in combination with durvalumab at 1500 mg on day 1 in a 28-day cycle. The primary end point was overall response rate (ORR) by RECIST (v1.1). To investigate markers predictive of clinical outcome, fresh tumor biopsies were obtained from all enrolled patients before treatment. **Results:** From August 2019 to May 2020, 30 MM patients (median # of lines, 2; range, 2 - 5) were enrolled. All enrolled patients were exposed to prior anti-PD-1 treatment (immediate failure, n = 23). The ORR was 30.0% (9 PRs, 10 SDs, 10 PDs), DCR 63.3%, median PFS 7.1 months (95% confidence interval (CI), 3.6-10.6), and median OS was 14.2 months (95% CI, 9.3-19.1). Common adverse events of any grade were anemia (n = 23, 76.7%), anorexia (n = 20, 66.7%) and thrombocytopenia (n = 19, 63.3%). Common adverse events of grade 3 or more included anemia (n = 10, 33.3%). One death occurred due to febrile neutropenia in a patient with a pre-existing wound infection. **Conclusions:** Ceralasertib in combination with durvalumab demonstrated a promising anti-tumor activity, particularly in melanoma patients who failed to standard of care including anti-PD1 treatment. Clinical trial information: NCT03780608. Research Sponsor: None.

9515 **Poster Discussion Session**

Clinical activity of fianlimab (REGN3767), a human anti-LAG-3 monoclonal antibody, combined with cemiplimab (anti-PD-1) in patients (pts) with advanced melanoma.

Omid Hamid, Ding Wang, Tae Min Kim, Sang-We Kim, Nehal J. Lakhani, Melissa Lynne Johnson, Roman Groisberg, Kyriakos P. Papadopoulos, John M. Kaczmar, Mark R. Middleton, Alexander I. Spira, Stephen K. Williamson, Guilherme Rabinowits, Rodolfo Gutierrez, Meredith McKean, Shuquan Chen, James Cassidy, Jayakumar Mani, Tasha Nicholle Sims, Glenn Kroog; The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA; Henry Ford Hospital, Detroit, MI; Seoul National University Hospital, Seoul, South Korea; University of Ulsan College of Medicine, Seoul, South Korea; START Midwest, Grand Rapids, MI; Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; START-San Antonio, San Antonio, TX; MUSC Hollings Cancer Center, Charleston, SC; University of Oxford, Oxford, United Kingdom; US Oncology Research/Virginia Cancer Specialists, Fairfax, VA; University of Kansas Medical Center, Westwood, KS; Miami Cancer Institute/Baptist Health South Florida, Miami, FL; The Angeles Clinical and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Fianlimab and cemiplimab are two high-affinity, fully human, hinge-stabilized IgG4 monoclonal antibodies. In a Phase 1 dose escalation study, fianlimab combined with cemiplimab showed an acceptable safety profile and some clinical activity in pts with advanced malignancies. Here, we present safety and clinical activity data from two expansion cohorts of pts with advanced melanoma (anti–programmed cell death/ligand-1 [anti–PD-(L)1] naïve or experienced) who were treated with fianlimab + cemiplimab and had an opportunity for first on-treatment tumor assessment (cut-off date: Jan 4, 2021). **Methods:** Pts with advanced melanoma who had no prior anti–PD-(L)1 treatment (naïve) or prior anti–PD-(L)1 treatment within 3 months of screening (experienced) received fianlimab 1600 mg + cemiplimab 350 mg by IV infusion every 3 weeks. Tumor measurements were performed every 6 weeks for the first 24 weeks and subsequently every 9 weeks per RECIST v1.1. **Results:** 48 pts with advanced melanoma were treated with the combination therapy: 33 were anti–PD-(L)1 naïve and 15 were anti–PD-(L)1 experienced (median age: 69 years vs 59 years; male: 66.7% vs 46.7%; Caucasian: 87.9% vs 60%). The safety profile (including immune-related adverse events [AEs]) of fianlimab + cemiplimab combination therapy was similar to that of anti–PD-1 monotherapy with one exception. The rate of adrenal insufficiency, 8.3% (4/48) of pts, is similar to the rate previously observed with anti–PD-1 + anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) combination therapy but higher than that observed with anti–PD-1 monotherapy. Grade ≥3 treatment-emergent AEs (TEAEs) occurred in 35.4% (17/48) of patients; Grade ≥3 serious TEAEs occurred in 22.9% (11/48) of patients; 8.3% (4/48) of patients discontinued treatment due to a TEAE. The most common TEAEs were fatigue (n = 15, 31.3%) and rash (n = 11, 22.9%). By investigator assessment, objective response rate (includes unconfirmed complete [CR] and partial responses [PR]) was 63.6% (3 CRs and 18 PRs) for anti–PD-(L)1 naïve pts and 13.3% (1 CR and 1 PR) for anti–PD-(L)1 experienced pts. Median progression-free survival and median duration of response for the anti–PD-(L)1 treatment naïve cohort have not been reached. Prognostic clinical markers and tumor biomarkers such as expression of LAG-3, PD-L1, and major histocompatibility complex II are being evaluated. Recruitment is ongoing. **Conclusions:** The safety profile of fianlimab + cemiplimab is similar to that observed with cemiplimab monotherapy and other anti–PD-1s, with the exception of higher rate of adrenal insufficiency. Fianlimab + cemiplimab combination has shown clinical activity for pts with advanced melanoma that is similar to anti–PD-1 + CTLA-4 combination therapy, but with lower demonstrated rates of TEAEs. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Two dosing regimens of nivolumab (NIVO) plus ipilimumab (IPI) for advanced (adv) melanoma: Three-year results of CheckMate 511.

Celeste Lebbe, Nicolas Meyer, Laurent Mortier, Ivan Marquez-Rodas, Caroline Robert, Piotr Rutkowski, Marcus O. Butler, Thomas Eigentler, Alexander M. Menzies, Michael Smylie, Ana Maria Arance, Paolo Antonio Ascierto, Inge Marie Svane, Mazhar Ajaz, Nikhil I. Khushalani, Maurice Lobo, Jesus Zoco, Jacopo Pigozzo; APHP Dermatology and CIC, U976, Université de Paris, Hôpital Saint-Louis, Paris, France; Institut Universitaire du Cancer de Toulouse and Centre Hospitalier Universitaire (CHU), Toulouse, France; Universite Lille, Centre Hospitalier Regional Universitaire de Lille, Lille, France; Medical Oncology, General University Hospital Gregorio Marañón & CIBERONC, Madrid, Spain; Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France; Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; University Hospital Tùbingen, Tübingen, Germany; Melanoma Institute Australia, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; Medical Oncology and Clinical Research, Cross Cancer Institute, Edmonton, AB, Canada; Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; Herlev Gentofte Hospital, Herlev, Denmark; Royal Surrey County Hospital, University of Surrey, Guildford, United Kingdom; Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center, Tampa, FL; Bristol Myers Squibb, Princeton, NJ; Syneos Health, Braine L'alleud, Belgium; Medical Oncology, IOV - Istituto Oncologico Veneto-IRCCS, Padua, Italy

Background: NIVO 1 mg/kg plus IPI 3 mg/kg (NIVO1 + IPI3) is approved for treatment (tx) of unresectable/adv melanoma, with demonstrated durable clinical benefit on long-term follow-up. Analysis of the phase 3b/4 CheckMate 511 study (NCT02714218) at 1 y showed that NIVO 3 mg/kg plus IPI 1 mg/kg (NIVO3 + IPI1) improves the safety profile of the combination; efficacy with the 2 regimens was similar in descriptive analyses. Here we present 3-y safety/efficacy results. **Methods:** Patients (pts) ≥ 18 y of age with previously untreated unresectable stage III/IV melanoma were randomized 1:1 to receive NIVO3 + IPI1 Q3W × 4 (N = 180) or NIVO1 + IPI3 Q3W × 4 (N = 178), both followed by NIVO 480 mg Q4W until progression/unacceptable toxicity. The primary endpoint was the incidence of grade (gr) 3–5 tx-related adverse events (TRAEs); secondary endpoints (descriptive analyses) included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The study was not powered to formally demonstrate noninferiority for efficacy endpoints. **Results:** At a median follow-up of 44.4 and 43.9 mo in the NIVO3 + IPI1 and NIVO1 + IPI3 groups, respectively, TRAEs led to tx discontinuation in 26% and 39% of pts; 57% and 42% of pts had received maintenance therapy. Gr 3–5 TRAE incidence remained significantly lower with NIVO3 + IPI1 than NIVO1 + IPI3 (33.9% vs 48.3%; odds ratio 0.55 [95% CI 0.36–0.84]). The most frequent TRAEs (any gr) were diarrhea (27%), fatigue (26%), and pruritus (26%) with NIVO3 + IPI1 and diarrhea (31%), pruritus (29%), and rash (27%) with NIVO1 + IPI3. In descriptive analyses, efficacy results were similar to those observed at 1 y. OS and tx-free–analysis outcomes were numerically similar in the 2 groups (table). **Conclusions:** At 3-y follow-up, NIVO3 + IPI1 continued to demonstrate an improved safety profile compared with NIVO1 + IPI3. In descriptive analyses, both groups demonstrated high 3-y OS rates that were numerically similar. This study provides important information regarding the benefit–risk profile of both dosing regimens of NIVO + IPI in pts with adv melanoma. Clinical trial information: NCT02714218. Research Sponsor: Bristol Myers Squibb.

Secondary endpoints	NIVO3 + IPI1 (N = 180)	NIVO1 + IPI3 (N = 178)	Stratified HR[a] (95% CI)
Investigator-assessed ORR, % (95% CI)	47 (40–55)	53 (45–60)	0.80[b] (0.53–1.21)
mPFS, mo (95% CI)	10.2 (6.2–21.9)	10.0 (6.3–40.9)	1.13 (0.85–1.50)
36-mo PFS rate, % (95% CI)	38 (30–46)	43 (35–50)	–
mOS, mo (95% CI)	NR (43.7–NR)	NR (40.8–NR)	1.03 (0.75–1.41)
36-mo OS rate, % (95% CI)	59 (51–66)	61 (53–67)	–
mTFI,[c,d] mo (range)	21.1 (0.2–48.9)[e]	22.6 (0.1–50.6)[f]	–
Pts alive and tx-free,[d,g] n (%)	72 (74)	72 (77)	–

[a]NIVO3 + IPI1 vs NIVO1 + IPI3. [b]Odds ratio. [c]Time from end of tx until subsequent cancer tx or last known date alive (if no subsequent cancer tx was received). [d]Post hoc analysis. [e]n = 132. [f]n = 127. [g]Pts free of study tx and subsequent systemic tx among those alive and in follow-up at database lock (n = 97 and 94). m, median; NR, not reached; TFI, tx-free interval.

9517 **Poster Discussion Session**

Avelumab in patients with previously treated Merkel cell carcinoma (JAVELIN Merkel 200): Updated overall survival data after more than five years of follow up.

Paul Nghiem, Shailender Bhatia, Andrew S. Brohl, Omid Hamid, Janice M. Mehnert, Patrick Terheyden, Kent C. Shih, Isaac Brownell, Celeste Lebbe, Karl D. Lewis, Gerald P. Linette, Michele Milella, Huiling Xiong, Guelseren Guezel, Sandra P. D'Angelo; University of Washington Medical Center at South Lake Union, Seattle, WA; University of Washington Medical Center, Seattle, WA; Moffitt Cancer Center, Tampa, FL; The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; University of Lübeck, Lübeck, Germany; Department of Medical Oncology, Tennessee Oncology, Nashville, TN; National Institutes of Health, Bethesda, MD; Université de Paris, INSERM U976 and CIC, AP-HP, Saint Louis Hospital, Paris, France; University of Colorado Denver School of Medicine, Aurora, CO; Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, PA; University of Verona School of Medicine and Verona University Hospital Trust (AOUI Verona), Verona, Italy; EMD Serono Research & Development Institute, Inc., an affiliate of Merck KGaA, Darmstadt, Germany, Billerica, MA; Merck KGaA, Darmstadt, Germany; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. Although MCC is considered chemosensitive, patients typically have limited survival benefit with chemotherapy. Before the approval of immune checkpoint inhibitors, patients with metastatic MCC (mMCC) had a poor prognosis, with a historical 5-year overall survival (OS) rate of approximately 14%. Avelumab (anti–PD-L1) became the first approved treatment for patients with mMCC, based on efficacy and safety data observed in the phase 2 JAVELIN Merkel 200 trial (NCT02155647), in which patients with mMCC received avelumab monotherapy. We report the long-term OS data from the cohort of patients with mMCC whose disease had progressed after ≥1 prior line of chemotherapy. **Methods:** Eligible patients had histologically confirmed, measurable (per RECIST 1.1) stage IV MCC. Patients received avelumab 10 mg/kg by intravenous infusion every 2 weeks until confirmed disease progression, unacceptable toxicity, or withdrawal. Long-term OS was analyzed; updated data for other efficacy endpoints, including response and progression-free survival, were not obtained. **Results:** A total of 88 patients were enrolled and received avelumab treatment. As of September 25, 2020 (data cutoff), median follow-up was 65.1 months (range, 60.8-74.1 months). Median OS was 12.6 months (95% CI, 7.5-17.1 months); the 48- and 60-month OS rates were 30% (95% CI, 20%-40%) and 26% (95% CI, 17%-36%), respectively. At data cutoff, treatment was ongoing in 1 patient (1.1%) and an additional patient (1.1%) had reinitiated avelumab after previously discontinuing treatment. Reasons for treatment discontinuation were disease progression (n = 45 [51.1%]), adverse event (AE; n = 11 [12.5%]), death (n = 10 [11.4%]), withdrawal of consent (n = 9 [10.2%]), loss to follow-up (n = 1 [1.1%]), protocol noncompliance (n = 1 [1.1%]), and other reason (n = 10 [11.4%]). At data cutoff, 19 patients (21.6%) had discontinued treatment but remained in follow-up, and 63 patients (71.6%) had died; causes of death were disease progression (n = 49 [55.7%]), unknown reason (n = 9 [10.2%]), AE not related to study treatment (n = 3 [3.4%]), and other reason (n = 2 [2.3%]). In total, 26 patients (29.5%) received subsequent anticancer therapy; the most common subsequent therapies after trial discontinuation were avelumab (n = 4 [4.5%]), carboplatin and etoposide (n = 4 [4.5%]), and pembrolizumab (n = 4 [4.5%]). **Conclusions:** Avelumab monotherapy led to meaningful long-term OS in a subset of patients with mMCC whose disease had progressed after chemotherapy. These results further support the role of avelumab as a standard-of-care treatment for patients with mMCC. Clinical trial information: NCT02155647. Research Sponsor: Funded by Merck KGaA, Darmstadt, Germany as part of an alliance between Merck KGaA and Pfizer.

9519 **Poster Discussion Session**

Intrathecal (IT) and intravenous (IV) nivolumab (N) for metastatic melanoma (MM) patients (pts) with leptomeningeal disease (LMD).

Ida John, Alexandra P. Foster, Cara L. Haymaker, Roland L. Bassett, J. Jack Lee, Michelle L. Rohlfs, Jessie Richard, Masood Iqbal, Ian E. McCutcheon, Sherise D. Ferguson, Amy B. Heimberger, Chantal M Saberian, Barbara Jane O'Brien, Sudhakar Tummala, Nandita Guha- Thakurta, Matthew Debnam, Hussein Abdul-Hassan Tawbi, Elizabeth M. Burton, Michael A. Davies, Isabella Claudia Glitza; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Neurosurgery, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX

Background: MM pts with LMD have a dismal prognosis, with median overall survival (OS) $<$ 3 months, no approved therapies and extremely limited clinical trial options. We previously reported initial safety findings from an open label, single arm, single center phase I/IB trial (NCT03025256), in which IT and IV N were well tolerated, without any CNS-specific or unexpected toxicity. Here we report an update on safety and maximum tolerated dose (MTD) for all patients enrolled, and efficacy for the completed dose cohorts. **Methods:** MM patients aged $>$18 with evidence of LMD by MRI and/or CSF cytology, ECOG PS $\leq$2 were treated with IT and IV N. Dexamethasone $\leq$4mg/daily and concurrent BRAF/MEK inhibitor(i) treatment was allowed. For cycle 1, IT N was administered via intraventricular reservoir on day (D)1. For subsequent cycles (every 14 days), pts received IT N on D1, followed by IV N 240 mg on D2. IT N doses evaluated were 5, 10, 20 mg and 50 mg. Blood and CSF were collected at multiple time points for translational research. The primary objectives of this first-in-human study were to determine the safety and MTD of IT N given with IV N in MM pts with LMD. Bayesian mTPI methodology was used to define the MTD. **Results:** To date, 23 pts have been treated: two at 5, three at 10, fourteen at 20 mg and four at 50 mg IT N. Median age at LMD diagnosis was 42 (28-73); 12 pts are male. All pts had radiographic evidence of LMD and neurological symptoms; 14 pts had positive CSF cytology at baseline. 21 pts received prior therapies for their metastatic melanoma: anti-PD1 (n = 19), BRAFi/MEKi (n = 14), chemo (n = 2), IT IL2 (n = 4) other (n = 2). 19 pts had prior XRT, including whole brain RT (n = 7). Two pts were treatment-naïve. The median number of IT N doses was five (1- 66). The combination regimen was well tolerated by all evaluable pts (n=23), with only five pts (22%) experiencing gr 3 AEs, and no reported gr 4 or 5 toxicities. Nausea (30%), diarrhea (26%), and rash (22%) were the most common AEs. Eight pts (23%) experienced AEs after IT N administration, all gr 1. Initial efficacy analysis included only pts (n=19) treated with first three dose levels (5-20mg). Median follow-up for these pts is 4.5 months (mos) (1.1, 31.5 mos) and median OS is 63 % at 3 mos, 42 % at 6 mos and 30% at 12 mos. **Conclusions:** The trial demonstrates the feasibility and safety of IT administration of modern immunotherapy for MM pts with LMD. No unexpected systemic or neurological toxicity was observed with 20mg IT N. 2 additional patients are required to complete the 50mg IT N cohort. OS rates at 6 and 12 mos are encouraging and support further evaluation of IT administration of immunotherapy agents for pts with MM and LMD. Final presentation will include results of LMD for all dose cohorts, composite response assessment and comparative analysis of longitudinal CSF samples to assess immunologic effects. Clinical trial information: NCT03025256. Research Sponsor: Bristol Myers Squibb.

9520 **Poster Discussion Session**

Phase II Study of TRIplet combination Nivolumab (N) with Dabrafenib (D) and Trametinib (T) (TRIDeNT) in patients (pts) with PD-1 naïve or refractory BRAF-mutated metastatic melanoma (MM) with or without active brain metastases.

Elizabeth M. Burton, Rodabe Navroze Amaria, Isabella Claudia Glitza, Denai R. Milton, Adi Diab, Sapna Pradyuman Patel, Jennifer Leigh McQuade, Virginia Honaker, Michael K.K. Wong, Patrick Hwu, Jennifer Ann Wargo, Michael A. Davies, Hussein Abdul-Hassan Tawbi; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Melanoma Medical Oncology, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX

Background: Targeted therapies (TT) & immunotherapies (IMT) have improved survival for pts with BRAF V600 mutated stage IV MM, however many pts still progress and ultimately die from their disease. Preclinical data support the rationale for combining TT and IMT, but trials evaluating triplet combinations in IMT-naïve pts have reported mixed results. Notably, pts with untreated brain metastases (BM) were excluded from prior triplet trials and have a median PFS of 5.6 months when treated with TT. Further, there remains an unmet need for effective therapies for pts after IMT failure, as retrospective studies have reported short median PFS (5 mos) for TT in this setting. We hypothesized that N in combination with DT is safe and will demonstrate clinical activity in BRAF-mutated pts naïve or refractory to PD1 therapy and in pts with BM. **Methods:** We conducted a single arm phase II study (NCT02910700) of NDT in pts with BRAF-mutated, unresectable stg III or stg IV MM. Prior IMT was allowed, but prior BRAF/MEKi was not. Pts with untreated BM and asymptomatic or mildly symptomatic/requiring steroids were also allowed. Pts received 3mg/kg IV Q2wks of N (later amended to 480 mg IV Q4wks), 150mg PO BID of D and 2mg PO QD of T, all starting on Day 1. The primary objective was to determine safety and efficacy (ORR by RECIST 1.1). Monitoring for safety and futility using Bayesian stopping rules was performed. Longitudinal tissue and blood samples were collected to perform correlative analyses. **Results:** Following a 6 pt safety run-in with no observed DLTs, 27 pts were treated w NDT. 17 pts were PD1 refractory, 10 were PD-1 naïve. 10 of these 27 pts had a history or presence of BM, including active BM. Median follow up was 18.4 months (range 3.2-45.9). ORR in 26 evaluable pts was 92% (3 CR, 21 PR). Among the PD1 refractory pts evaluable for response (n = 16), ORR was 88% (2 CRs, 12 PR). All 10 evaluable PD-1 naïve pts achieved a response. 4 of 7 evaluable pts w BM achieved an intracranial response (57%), including 2 CRs. The median PFS for all pts was 8.5mos (8.5mos in PD1 naïve pts, 8.2mos in PD1 refractory pts). Median PFS for pts without BM was 8.5mos, 8.0 mos for those with BM. Median OS for all pts was not reached, and no statistically significantly difference in OS by PD1 exposure or presence of BM. 78% of pts experienced treatment related grade 3/4 AEs and 6 pts (22%) discontinued all 3 drugs due to toxicities. **Conclusions:** NDT at full doses of all 3 agents has a toxicity profile consistent with previously reported triplet combinations and shows promising clinical activity in pts with IMT refractory disease and with BM. There were no significant differences in outcomes between pts with and without BM. Translational studies to delineate predictors and mechanisms of response and resistance are ongoing. Clinical trial information: NCT02910700. Research Sponsor: BMS.

9521 **Poster Discussion Session**

An immunogenomic analysis of melanoma brain metastases (MBM) compared to extracranial metastases (ECM).

Lucy Kennedy, Amanda E.D. Van Swearingen, Jeff Sheng, Dadong Zhang, Xiaodi Qin, Eric S. Lipp, Swaminathan Kumar, Gao Zhang, Brent Allen Hanks, Michael A. Davies, Kouros Owzar, Carey K. Anders, April K.S. Salama; Duke University Medical Center, Durham, NC; Duke Center for Brain and Spinal Metastases, Duke University Medical Center, Durham, NC; The University of Texas MD Anderson Cancer Center, Houston, TX; Duke University Medical Center, Duke Cancer Institute, Durham, NC; Duke University, Durham, NC

Background: Previous work has shown that MBM have a unique molecular profile compared to ECM. Description of the biology of MBM will facilitate the design of rational therapies for patients (pts) with MBM. **Methods:** We analyzed a previously published dataset from MD Anderson Cancer Center, which includes RNA-seq on surgically resected FFPE MBM (88 tumors from 74 pts) and surgically resected ECM from the same pts (50 from 34 pts). WES on 18 matched pairs of MBM and ECM was available. The STAR pipeline was used to estimate mRNA abundance. The DESeq2 package was used to perform differential gene expression (DGE) analyses. Pathway analysis was performed using Gene Set Enrichment Analysis (GSEA). Paired DGE and GSEA analyses comparing MBM vs. lymph node metastases (LN mets, n = 16) and MBM vs. skin mets (n = 10) were performed. CIBERSORT estimated relative abundance of immune cell types in MBM and ECM. The GATK Mutect2 pipeline was used to call somatic mutations using paired normal tumor samples. Mutations were annotated using the Ensembl Variant Effect Predictor and visualized using the Maftools package in R. RNA-seq was available on 54 primary cutaneous melanoma (CM) pt samples, including 19 CM which did not recur, 19 CM which recurred as MBM, and 16 CM which recurred as ECM. Gene Ontology or KEGG Pathway analysis was performed using goana function of limma package in R. **Results:** Comparing MBM vs. LN and MBM vs. skin mets, paired DGE identified 136 and 89 up-regulated genes with a fold change > 2 and false-discovery rate (FDR) q-value < 0.05. Moreover, 308 and 659 down-regulated genes with a fold change < 0.5 were identified in MBM vs. LN and MBM vs. skin mets, respectively ($q < 0.05$). Paired GSEA found that autophagy signaling pathways may be up-regulated in MBM vs. LN and MBM vs. skin mets. On a single-gene level, comparing both MBM vs. LN and skin mets, the most strongly up-regulated genes in autophagy pathways were GFAP and HBB, whereas fold changes in the majority of other autophagy-related genes were low and did not reach significance. Comparison between CM which recurred in brain vs. CM which did not recur identified up-regulation of autophagy pathways. No difference in autophagy pathway expression was observed comparing between CM with any recurrence vs. without recurrence. CIBERSORT identified an increased proportion of immune suppressive M2 macrophages compared to tumor suppressive M1 macrophages in both MBMs and ECMs. **Conclusions:** Up-regulation of autophagy pathways was observed in pt-matched MBM vs. LN and skin mets. This finding seemed to be driven by up-regulation of GFAP and HBB, which could reflect changes in the tumor microenvironment (TME). Future studies using single-cell RNA-seq or spatial transcriptomic technology will dissect the TME. A higher M2:M1 ratio may contribute to an immune suppressive tumor microenvironment in MBM and ECM and is targetable. Validation of our findings in an independent Duke dataset is ongoing. Research Sponsor: None.

9522 **Poster Discussion Session**

Characterizing the tumor and immune landscape of melanoma patients treated with combined checkpoint blockade and MAPK targeted therapy.

Liron Zisman, Donald P. Lawrence, David F. McDermott, Mofei Liu, Elizabeth Iannotti Buchbinder, Irena Gushterova, Anna L. K. Goyne, Justine Vanessa Cohen, David Michael Miller, Thomas LaSalle, Emily Blaum, Dennie T. Frederick, Tatyana Sharova, Genevieve Marie Boland, Anita Giobbie-Hurder, Moshe Sade-Feldman, Keren Yizhak, Nir Hacohen, Ryan J. Sullivan; Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel; Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; Division of Biostatistics, Department of Data Science, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; The Johns Hopkins University School of Medicine, Baltimore, MD; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Surgical Oncology, Boston, MA; Dana-Farber Cancer Institute, Boston, MA

Background: Melanoma therapy has been revolutionized by two novel therapeutic approaches: mitogen activated protein kinase (MAPK) targeted therapy (MTT) and immune checkpoint blockade therapy (ICB). Less than half of patients respond to ICB monotherapy, in part due to non-responsive tumor microenvironment (TME). It previously has been shown that MTT enhances anti-tumor immunity within the TME, thus providing a strong rationale for its combination with immunotherapy. Regimens combining MTT with ICB have had mixed results, and which patients should be treated with these combinations is unknown. **Methods:** The first arm (NCT03149029) of a planned two stage design was to enroll 14 patients (pts) harboring $BRAF^{V600}$ mutation treated with 2 weeks (wks) of MTT (dabrafenib plus trametinib) then 6 wks of concomitant MTT and pembrolizumab, followed by single-agent pembrolizumab thereafter. The primary endpoint is clinical benefit (CB) defined as partial/complete response or stable disease (per RECIST1.1) persisting at 24 wks. If 9 of 14 pts had CB, then 11 more pts would be enrolled for a total cohort of 25. Serial biopsies were performed prior to MTT, following the 2-week lead-in of MTT, and following six wks of combination immune therapy and MTT. Single-cell RNA-seq profiling of $CD45^{+}$ and $CD45^{-}$ cells was performed using both the smart-seq2 plate-based protocol and 10x genomics platform. **Results:** Sixteen pts were enrolled, with 14 receiving both MTT and ICB. Two pts did not receive ICB due to MTT toxicity. Only 5 had CB, and the second stage did not open. A 6^{th} pt had CB extracranially with a new small brain met at wk 24 scans was considered CB for tumor analysis. A clustering analysis of 25 samples (n = 9 pts) showed that following MTT the abundance of CD8 T-cells as well as tumor IFNγ levels were significantly elevated in CB vs. no CB (NCB) patients. In addition, tumor associated macrophages (TAM) in NCB patients possessed mainly an M2 phenotype and expressed a significantly higher level of immune suppressor genes, such as HLA-G and CD52. Interestingly, NCB pts had a significantly higher expression of tumor TGFβ, which is a strong inducer of M2 macrophages. In contrast, most of the TAMs occupying the tumor of the CB pts had the M1 phenotype, and significantly expressed CD9, CD81 and CD82, important factors during antigen recognition and immunological synapse formation. **Conclusions:** Abbreviated MTT with ICB did not lead to increased clinical benefit at 24 wks in this small study. It is theorized that the tumor's ability to create a unique microenvironment by producing certain factors (e.g. TGFβ), modifies the immune system and may tilt its path into immune suppression thereby reducing the efficacy of this combinatorial therapy in melanoma pts with metastatic disease. These results may help identify pts most likely to benefit from combined MTT plus ICB and new targets to overcome resistance to these regimens. Clinical trial information: NCT03149029. Research Sponsor: Merck, U.S. National Institutes of Health.

9523 **Poster Discussion Session**

Effects of baseline lactate dehydrogenase (LDH), interferon gamma (IFN-g) expression, and tumor mutational burden (TMB) on treatment response to first-line atezolizumab (A) + vemurafenib (V) and cobimetinib (C) in *BRAF*^{V600} mutation–positive advanced melanoma.

Caroline Robert, Karl D. Lewis, Paolo Antonio Ascierto, Rodrigo Ramella Munhoz, Gabriella Liszkay, Luis de la Cruz-Merino, Judit Olah, Paola Queirolo, Jacek Mackiewicz, Ivor Caro, Kalpit Shah, Harper Forbes, Haocheng Li, Christian Hertig, Yibing Yan, Edward Francis Mckenna, Ralf Gutzmer, Grant A. McArthur; Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France; University of Colorado Comprehensive Cancer Center, Aurora, CO; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; Országos Onkológiai Intézet, Budapest, Hungary; Hospital Universitario Virgen Macarena, Seville, Spain; University of Szeged Szent-Györgyi Medical University, Szeged, Hungary; IRCCS Istituto Europeo di Oncologia, Milan, Italy; Department of Diagnostics and Cancer Immunology, Greater Poland Cancer Centre, Poznan, Poland; Genentech, Inc., South San Francisco, CA; Hoffmann La-Roche Ltd., Mississauga, ON, Canada; F. Hoffmann-La Roche Ltd., Basel, Switzerland; Haut-Tumour-Zentrum Hannover (HTZH), Klinik für Dermatologie, Allergologie und Venerologie, Medizinische Hochschule Hannover (MHH), Hannover, Germany; Melanoma and Skin Service and Cancer Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: The phase 3 IMspire150 study showed that first-line A+V+C improved investigator-assessed PFS vs placebo (P)+V+C in *BRAF*$^{V600E/K}$ mutation–positive advanced melanoma (hazard ratio 0.78; *P*=.0249). Prior biomarker analyses showed that IFN-g or TMB $>$ 10 mut/Mb were associated with greater PFS benefits with A+V+C (Lewis et al. *J ImmunoTher Cancer* 2020;8:A188-A189). We further evaluated the association of these biomarkers with outcomes. **Methods:** Exploratory recursive partitioning analysis (RPA) was used to model associations between PFS and age ($<$ 65 vs $\geq$65 y), Eastern Cooperative Oncology Group performance status (0 vs 1), liver metastases (yes vs no), metastatic sites ($\leq$3 vs $>$ 3), sum of longest tumor diameters ($<$ 44 mm vs $\geq$44 mm), baseline LDH (normal [n] vs elevated [e]), TMB ($<$ 10 vs $\geq$10 mut/Mb), PD-L1 (negative vs positive), and IFN-g (high [h; $>$ Quartile 3; Q3] vs intermediate [$>$ Q1 and $\leq$Q3] vs low [$\leq$Q1]). Time-to-event analyses were summarized using Kaplan-Meier estimates. **Results:** The RPA analysis included 208/256 (81.3%) patients (pts) from the A+V+C arm of IMspire150 for whom LDH, TMB, IFN-g, and PD-L1 data were available. RPA showed that LDH was associated with PFS. In pts treated with A+V+C and n-LDH, h-IFN-g signature was associated with longer PFS and higher rates of objective response (OR) and complete response (CR) vs low/intermediate (l/i) IFN-g (2-y PFS: 59% vs 38%; ORR: 77% vs 69%; CR: 38% vs 15%, respectively); TMB $\geq$10 mut/Mb was associated with more favorable outcomes in pts with e-LDH (Table). In contrast, neither IFN-g nor TMB discriminated PFS outcomes in n-LDH or e-LDH pt subgroups receiving P+V+C. Pts with e-LDH and TMB $<$ 10 mut/Mb had poor PFS outcomes, with 2-y PFS rates of 9% and 3% and lower rates of OR (51% and 62%) and CR (5% and 9%) in the A+V+C and P+V+C arms, respectively. Similar trends were observed for duration of response (DOR), and for the subset of pts with *BRAF*^{V600E} mutation–positive melanoma. A+V+C improved PFS vs P+V+C across all subgroups with the exception of e-LDH and TMB $<$ 10. **Conclusions:** IFN-g and TMB discriminated PFS benefit in pts receiving A+V+C but not for those receiving P+V+C. Durable responses were observed for pts treated with A+V+C in the n-LDH + h-IFNg subgroups. Research Sponsor: F. Hoffmann-La Roche.

	n-LDH + h-IFN-gamma	n-LDH + l/i-IFN-gamma	e-LDH + TMB ≥10	e-LDH + TMB < 10
A+V+C, n	26	110	35	37
Median PFS, mo (95% CI)	Not estimable (NE; 15.3-NE)	16.6 (11.1-23.0)	11.4 (6.2-NE)	5.6 (4.3-10.6)
Median DOR, mo (95% CI)	NE (16.8-NE)	20.4 (14.8-NE)	14.8 (10.4-NE)	9.0 (4.5-NE)
P+V+C, n	47	94	32	32
Median PFS, mo (95% CI)	12.9 (10.1-18.9)	12.5 (9.5-21.3)	7.3 (5.6-16.9)	7.6 (6.1-11.1)
Median DOR, mo (95% CI)	12.0 (9.4-NE)	18.7 (11.1-NE)	14.5 (7.7-NE)	7.7 (5.7-14.5)

TMB and *BRAF* mutation status are independent predictive factors in stage IIIC/D/IV melanoma patients receiving adjuvant PD-1 antibodies.

Andrea Forschner, Julia Eckardt, Peter Martus, Sorin Armeanu-Ebinger, Stephan Ossowski, Irina Bonzheim, Thomas Eigentler, Teresa Maria Santos Amaral, Lukas Flatz, Claus Garbe, Christopher Schroeder; Department of Dermatology, University Hospital of Tuebingen, Tuebingen, Germany; Institute for Clinical Epidemiology and Applied Biometrics, University Hospital Tübingen, Tübingen, Germany; Institute for Medical Genetics and Applied Genomics University Hospital Tuebingen, Tübingen, Germany; Institute of Pathology and Neuropathology, University Hospital Tübingen, Tübingen, Germany, Tübingen, Germany; Department of Dermatology, University Hospital Tübingen, Tübingen, Germany; Department of Dermatology, University of Tübingen, Tübingen, Germany

Background: High tumor mutational burden (TMB) is associated with a favorable outcome in metastatic melanoma patients treated with immune checkpoint inhibitors. However, data are limited in the adjuvant setting. As BRAF mutated patients have an alternative with targeted adjuvant therapy, it is important to identify predictive factors for relapse and recurrence-free survival (RFS) in patients receiving adjuvant PD-1 antibodies. **Methods:** We systematically evaluated all melanoma patients who started adjuvant PD-1 antibody therapy at our center between March 2018 and September 2019 to identify predictive factors for outcome. The median follow-up time from start of adjuvant anti-PD-1 therapy was 22 months. Tumor and normal tissue of all stage IIIC/D/IV patients and of stage IIIA/B patients with relapse were sequenced using a 700 genes panel. Predictive factors for relapse and RFS were identified using univariate and multivariate logistic and Cox regression analysis. RFS was estimated by the Kaplan-Meier method. TMB high was defined as the top 20 % of the cohort, corresponding to TMB values $\geq$ 20 Var/Mb. **Results:** A total of 165 patients were included in this study. According to AJCC 8th the initial tumor stages at the beginning of adjuvant anti-PD-1 therapy were as follows: N = 80 stage IIIA/B (48 %), N = 85 stage IIIC/D/IV (52 %). 72/165 patients (44 %) suffered a relapse, 44/72 (61 %) with loco regional and 28/72 (39 %) with distant metastases. Sequencing results were available from 79 / 85 patients with stage IIIC/D/IV. Here we present the results of this cohort. TMB low (OR 17.46, 95%CI 4.03-75.55; $p < 0.0001$) or absence of BRAF V600E/K mutation (OR 4.13, 95%CI 1.36-12.53; $p = 0.012$) were statistically significant, independent predictive factors for relapse. Also, with regard to RFS, BRAF mutation status and TMB were statistically significant and independent predictive factors. In the table below we display results for the combined variables. Patients with BRAF V600E/K mutation and TMB high had the best outcome. **Conclusions:** We identified TMB high as positive predictive marker in stage IIIC/D/IVmelanoma patients with adjuvant PD-1 antibody therapy. In tumors with *BRAF* V600E/K mutation and concurrent low TMB, adjuvant targeted therapy with BRAF- and MEK-inhibitors may be an alternative. This is also supported by the data on adjuvant dabrafenib and trametinib, which showed a greater advantage in patients with low TMB, presumably due to less tumor heterogeneity. Research Sponsor: None.

Characteristic	No relapse N = 34	Relapse N = 45	p	1-year RFS (%; 95%CI)	2-year RFS (%; 95%CI)	P
BRAF V600E/K mutation + TMB high	4	0	< 0.0001	100	100	< 0.0001
No BRAF V600E/K mutation + TMB high	11	3		86 (67-100)	78 (56-100)	
BRAF V600E/K mutation + TMB low	12	13		56 (37-75)	42 (20-65)	
No BRAF V600E/K mutation + TMB low	7	29		33 (18-49)	19 (6-32)	

9525 **Poster Session**

Improved pyrexia-related outcomes associated with an adapted pyrexia adverse event (AE) management algorithm in patients (pts) treated with adjuvant dabrafenib + trametinib (dab + tram): Primary results of COMBI-APlus.

Victoria Atkinson, Caroline Robert, Jean-Jacques Grob, Helen Gogas, Caroline Dutriaux, Lev V. Demidov, Avinash Gupta, Alexander M. Menzies, Bettina Ryll, Flora Miranda, Hiya Banerjee, Mike R. Lau, Michele Del Vecchio; Princess Alexandra Hospital, University of Queensland, Greenslopes, Brisbane, QLD, Australia; Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; Aix-Marseille University, Marseille, France; National and Kapodistrian University of Athens, Athens, Greece; Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France; N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation; The Christie NHS Foundation Trust, Manchester, United Kingdom; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Melanoma Patient Network Europe, Uppsala, Sweden; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The long-term benefit of adjuvant dab + tram in pts with resected stage III *BRAF* V600E/K–mutant melanoma was demonstrated in COMBI-AD where AEs led to permanent discontinuation of dab + tram in 26% of pts, most often due to pyrexia (9%). The COMBI-APlus trial (NCT03551626) is designed to evaluate whether an adapted pyrexia management algorithm could reduce high-grade pyrexia and other pyrexia-related adverse outcomes, such as treatment cessation and hospitalization. **Methods:** COMBI-APlus is an open-label, Phase IIIb trial evaluating an adapted pyrexia management algorithm in pts with high-risk resected stage III BRAF V600E/K–mutant melanoma treated with 12 mo of adjuvant dab + tram. In the adapted algorithm, both dab and tram were interrupted promptly at the onset of pyrexia (temperature $\geq 38^{\circ}$C). In the event of suspected recurrent pyrexia, treatment may be interrupted in the presence of pyrexia syndrome (ie, chills, rigors, night sweats, or influenza-like symptoms without temperature $\geq 38^{\circ}$C) at investigator discretion. Treatment with dab + tram was restarted at the same dose level once pts were symptom free for $\geq$ 24 hours. The primary endpoint is the composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent discontinuation due to pyrexia vs a historical control from COMBI-AD (20%; 95% CI, 16.3%-24.1%). Secondary endpoints include relapse-free survival (RFS) and safety. **Results:** A total of 552 pts were enrolled. At the data cutoff (5 Oct 2020), all pts had completed 12 mo of treatment; median duration of follow-up was 18.4 mo. COMBI-APlus met its primary endpoint of significant improvement in composite rate of pyrexia. The composite rate was 8.0% (95% CI, 5.9%-10.6%), with rates of 3.8% for grade 3/4 pyrexia, 4.3% for hospitalization due to pyrexia, and 2.4% for discontinuation due to pyrexia. The estimated 12-mo RFS rate was 91.8% (95% CI, 89.0%-93.9%). The most common AEs ($\geq$ 20%) were pyrexia (67.8%), headache (31.7%), blood creatine phosphokinase increase (27.9%), diarrhoea (27.0%), chills (26.4%), fatigue (25.7%), asthenia (23.6%), nausea (23.4%), rash (21.4%), and arthralgia (21.0%). AEs of any type led to permanent dab + tram discontinuation in 14.7% of pts. **Conclusions:** This primary analysis suggests the new adapted pyrexia management algorithm is effective in reducing grade 3/4 pyrexia, pyrexia-related hospitalization, and treatment discontinuation in pts receiving adjuvant dab + tram. The early efficacy appears consistent with that observed in COMBI-AD. The growing experience of oncologists in managing pyrexia with this simple algorithm may reduce the need for hospitalization or visits to a healthcare provider, which is highly desirable during the current COVID-19 pandemic. Thus, more pts can remain on treatment and derive benefit. Clinical trial information: NCT03551626. Research Sponsor: Novartis.

9526 **Poster Session**

Overall survival in patients who received checkpoint inhibitors after completing tebentafusp in a phase 3 randomized trial of first-line metastatic uveal melanoma.

Marlana Orloff, Richard D. Carvajal, Alexander Noor Shoushtari, Joseph J. Sacco, Max Schlaak, Claire Watkins, Shaad Essa Abdullah, Howard Goodall, Marcus O. Butler; Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA; Department of Medicine, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Clatterbridge Cancer Centre, Merseyside, United Kingdom; University Hospital, Department of Dermatology and Allergy, LMU Munich, Munich, Germany; Clarostat Consulting Limited, Bollington, United Kingdom; Immunocore, Abingdon, United Kingdom; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Tebentafusp (tebe) is a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells. Tebe significantly improved OS compared to investigator's choice (IC) in first line (1L) mUM [NCT03070392]. In a phase (ph) 2 study of tebe in 2L+ mUM (NCT02570308), several checkpoint inhibitor (CPI) refractory pts who were re-treated with CPI after tebe achieved durable clinical benefit [1]. We therefore evaluated clinical outcomes of post-tebe CPI in patients treated on the ph3 trial of tebe versus investigator's choice (IC) [NCT03070392]. **Methods:** In the ph3 trial, 378 HLA-A*02:01+ 1L mUM pts were randomized 2:1 to tebe (n=252) or IC (n=126) [pembrolizumab (82%), ipilimumab (12%) or dacarbazine (6%)]. No crossover to tebe was permitted, investigators were free to choose subsequent therapy, and there was no re-randomization at time of subsequent therapy. This analysis was conducted on the first interim analysis (data extracted Nov-2020). When pts received more than one subsequent therapy, the first was used in these analyses. Medians and 1-yr OS from the start of post-study therapy are obtained from standard Kaplan-Meier analyses; hazard ratios (HR) are from Cox regression models adjusted for age and gender. **Results:** 106/252 (42%) tebe pts received ≥ 1 subsequent therapy: 35% CPI, 9% chemo, 6% liver directed therapy (LDT), 6% other. 55/126 (44%) of IC pts received ≥ 1 subsequent therapy: 21% CPI, 10% chemo, 12% LDT, 10% other. Median time to first subsequent therapy was longer for tebe pts at 5.2 mo vs. IC pts at 3.8 mo. The median duration from start of first subsequent CPI to end date was longer in the prior tebe pts at 4 mo vs prior IC pts at 2.8 mo. From the start of any first subsequent therapy, prior tebe pts had longer OS compared to prior IC pts, HR 0.67 (95% CI 0.42, 1.07). Most of the subsequent therapy was CPI, and the OS benefit was also seen in this subset, HR 0.62 (95% CI 0.34, 1.14). For prior tebe pts, the median and 1-yr OS rates from start of any first subsequent therapy were 13 mo and 53% and from start of first subsequent CPI were 16 mo and 63%. Both were higher than the sequence of IC followed by any therapy (11 mo and 44%), IC followed by CPI (9 mo and 47%) and a recent meta-analysis of 2L+ mUM (7 mo and ~35% 1-yr OS rate). **Conclusions:** Pts who progressed on tebe and then received CPI had better OS compared to pts who progressed on IC and then received CPI. Further analysis will explore whether confounding factors are influencing this effect. These exploratory data suggest that tebe, relative to IC, may improve outcomes to subsequent CPI. (1)Yang J. et al. ASCO 2019, *J. ClinOncol* 37:15_suppl, 9592. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9527 **Poster Session**

Co-primary endpoint of overall survival for tebentafusp (tebe)-induced rash in a phase 3 randomized trial comparing tebe versus investigator's choice (IC) in first-line metastatic uveal melanoma.

Jessica Cecile Hassel, Piotr Rutkowski, Jean-Francois Baurain, Marcus O. Butler, Max Schlaak, Ryan Sullivan, Sebastian Ochsenreither, Reinhard Dummer, John M. Kirkwood, Anthony M. Joshua, Joseph J. Sacco, Alexander Noor Shoushtari, Marlana Orloff, Richard D. Carvajal, Omid Hamid, Shaad Essa Abdullah, Chris Holland, Howard Goodall, Paul Nathan, Sophie Piperno-Neumann; Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Institut Roi Albert II Cliniques Universitaires St-Luc, Brussels, Belgium; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; University Hospital, Department of Dermatology and Allergy, LMU Munich, Munich, Germany; Massachusetts General Hospital, Boston, MA; Charité Comprehensive Cancer Center, Berlin, Germany; Skin Cancer Center, University Hospital of Zürich, Zürich, Switzerland; University of Pittsburgh Medical Center, Pittsburgh, PA; Kinghorn Cancer Centre, St Vincent's Hospital, Darlinghurst, NSW, Australia; Clatterbridge Cancer Centre, Merseyside, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA; Department of Medicine, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY; The Angeles Clinic and Research Institute, Los Angeles, CA; Immunocore, Abingdon, United Kingdom; Mount Vernon Cancer Centre, London, United Kingdom; Institut Curie, Paris, France

Background: Tebe is a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells. In this Phase (Ph) 3, randomized trial of first line (1L) metastatic uveal melanoma (mUM) [NCT03070392], tebe significantly improved overall survival (OS) vs. investigator's choice (IC) in the intention-to-treat population (ITT). In previous trials, tebe-related skin adverse events (AEs), hypothesized to be on-target, off-tumor activity against gp100-expressing melanocytes, were associated with improved OS. This association was tested prospectively as a co-primary endpoint in the Ph3 study. **Methods:** 378 1L HLA-A*02:01+ mUM pts were randomized 2:1 to tebe (n = 252) or IC (n = 126). Co-primary endpoints were 1) OS in all randomized pts (ITT) and 2) OS in tebe-randomized pts who develop any grade rash in week (wk) 1 vs. all receiving IC. Rash was defined as composite of preferred AE terms. Melanocyte-related AEs (MRAEs) were defined as pigment change AEs in the skin or hair. Overall study-wide alpha was controlled at 0.05, with 90% assigned to ITT and 10% to rash. This analysis was conducted on the first interim analysis (data extracted Nov-2020). **Results:** In the 245 tebe treated pts, the characteristic skin related AEs included most frequently rash (at any time) in 201 pts (82%), pruritis in 167 pts (68%), MRAEs in 109 pts (45%) and erythema in 69 pts (28%). While rash, erythema and pruritis mostly occurred in the first 4 weeks, MRAEs occurred after a median of 2.7 mo. Rash captures most pts, 201/227 (89%), who have any of these skin related AEs. Rash occurred in 146 pts (60%) by wk 1; 179 pts (73%) by wk 2; and 195 pts (80%) by wk 3. Tebe pts with wk 1 rash had significantly longer OS vs. the IC arm, HR 0.35 (95% CI 0.23, 0.53), $p < 0.0001$. The estimated 1-yr OS rates were 83% vs 58%, respectively. When expanded to include tebe pts with rash through wk 3, the 1-yr OS rate of 75% was still numerically higher than IC. The 50 (20%) tebe pts who did not experience rash by week 3 had 1-yr OS rate of 55%. **Conclusions:** In 1L mUM pts, tebe significantly improved OS compared to IC in the ITT analysis. Week 1 rash, presumed due to tebe redirection of T cells to gp100+ skin melanocytes, was associated with a very strong OS benefit. Therefore, rash may be a marker that the immune system can be mobilized by tebe to target gp100+ cells. The vast majority of tebe pts will develop a rash at some point, and tebe pts without rash may still derive benefit. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9528 **Poster Session**

Results of phase II randomized study of intermittent versus continuous schedule of vemurafenib plus cobimetinib in BRAF-mutated advanced melanoma.

Maria Gonzalez-Cao, Clara Mayo de las Casas, Juana Oramas, Miguel-Angel Berciano-Guerrero, Luis De la Cruz, Pablo Cerezuela-Fuentes, Ana Maria Arance, Eva Muñoz-Couselo, Enrique Espinosa, Teresa Puértolas, Robert Diaz Beveridge, Sebastian Ochenduszko, Maria Jose Villanueva Silva, Laura Basterretxea, Lorena Bellido, Delvys Rodriguez-Abreu, Ana Drozdowskyj, Miguel Angel Molina Vila, Jose Antonio Lopez-Martin, Alfonso Berrocal, Spanish Melanoma Group (GEM); Instituto Oncológico Dr. Rosell, Barcelona, Spain; Pangaea Oncology, Barcelona, Spain; Hospital Universitario de Canarias, Tenerife, Spain; Unidad Intercentros de Oncología. HURyVV (Hospitales Universitarios Regional y Virgen de la Victoria de Málaga), IBIMA (Instituto de Investigación Biomédica de Málaga), Málaga, Spain; Hospital Universitario Virgen Macarena, Seville, Spain; Medical Oncology. Hospital Virgen de la Arrixaca, Murcia, Spain; Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Vall d'Hebron Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Department of Medical Oncology, La Paz University Hospital, Madrid, Spain; Medical Oncology. Hospital Miguel Servet, Zaragoza, Spain, Zaragoza, Spain; Hospital Universitari i Polit?cnic La Fe, Valencia, Spain; Hospital Universitario Dr. Peset, Valencia, Spain; Complexo Hospitalario Universitario de Vigo, Vigo, Spain; Hospital Universitario de Donostia, San Sebastian, Spain; Hospital Universitario de Salamanca, Salamanca, Spain; Hospital Universitario Insular de Gran Canaria, Las Palmas De Gran Canaria, Spain; Oncology Department, Instituto Oncologico Dr Rosell, Hospital Universitari Dexeus, Barcelona, Spain; Hospital 12 de Octubre, Madrid, Spain; Hospital General Universitario de Valencia, Valencia, Spain

Background: Combination of vemurafenib plus cobimetinib is approved for the treatment of BRAF-mutated advanced melanoma. Although patients initially respond to treatment, resistance emerges before 18 months in most cases. One of the key pre-clinical observations that supported an intermittent schedule was that resistant tumors suffer a fitness deficit in the absence of the drug, so modulation of the drug pressure through an intermittent dosing could delay the emergence of resistance. **Methods:** GEM1501 is a randomized phase 2 study comparing the activity of the combination of vemurafenib 960 mg every 12 h/d plus cobimetinib 60 mg/d in a standard (arm A) versus intermittent schedule (arm B). Arm A: four-week (w) cycles of daily vemurafenib for 4w plus cobimetinib for 3w-on and 1w-off-treatment. Arm B: first three cycles according to the standard schedule, followed by 6w-cycle with 2w-off vemurafenib & 3w-off cobimetinib. Primary endpoint was progression free survival (PFS) and secondary were objective response (OR) and treatment-related adverse events (TAEs). **Results:** 70 treatment-naïve patients were included. Results in arms A and B: median PFS 16.2 (95%CI 9.5, 24.1) vs 6.9 months (95%CI 5.2, 9.3) (p = 0.079)**;** OR in 25 (71.4%) (8 complete -23%-) vs 21 (60%) patients (5 complete -14%-); G3-4 TAEs 42.8% vs 40.0%, respectively. Analysis of *BRAF*^{V600} mutation in tumoral cell free DNA (cfDNA) was performed in serial plasma samples in 41 patients. Twenty-one (51%) patients had detectable *BRAF*^{V600} mutation in pretreatment cfDNA (preBRAF+). Significant differences in PFS were found according to preBRAF^{V600}: 8.2 months (95%CI 5.2, 13.6) in preBRAF+ vs non-reached (NR) (95%CI 2.8, NR) in preBRAF- (p = 0.017). In arm A, median PFS was 13.3 months (95% CI 4.6, NR) in preBRAF+ vs NR (95% CI 2.3, NR) in preBRAF-. In arm B, median PFS was 6.2 months (95% CI 0.3-8.3) in preBRAF+ vs NR (95%CI 2.8, NR) in preBRAF- (p = 0.003)**.** *BRAF*^{V600} mutation became undetectable in cfDNA after treatment initiation in all preBRAF+ patients. Different kinetic of *BRAF*^{V600} mutation in cfDNA was found according to treatment arm. At progression, *BRAF*^{V600} reappeared in cfDNA in all (5/5) cases treated in arm B, but only in 50% (3/6) of cases in arm A. NGS analysis of cfDNA at progression suggested different resistance mechanisms. **Conclusions:** The results of this study do not support the use of an intermittent schedule of vemurafenib plus cobimetinib in advanced melanoma. *BRAF*^{V600} detection in pretreatment cfDNA is a prognostic factor of poor survival that it is independent of treatment schedule, although most striking differences favoring continuous arm vs intermittent arm were found in patients with detectable *BRAF*^{V600} mutation on pretreatment cfDNA. Further research is required to determine the clinical value of the analysis of resistance mechanisms in cfDNA. Clinical trial information: 2014-005277-36. Research Sponsor: Spanish Melanoma Group, Pharmaceutical/Biotech Company.

9529 **Poster Session**

A phase 2 clinical trial on trametinib and low-dose dabrafenib in advanced pretreated *BRAF*^{V600}/*NRAS*$^{Q61R/K/L}$ wild-type melanoma (TraMel-WT): Interim efficacy and safety results.

Gil Awada, Julia Katharina Schwarze, Jens Tijtgat, Giuseppe Fasolino, Hendrik Everaert, Bart Neyns; Department of Medical Oncology, Universitair Ziekenhuis Brussel, Brussels, Belgium; Department of Ophthalmology, Universitair Ziekenhuis Brussel, Brussels, Belgium; Department of Nuclear Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium

Background: The mitogen-activated protein kinase (MAPK) pathway can be activated by alternative driver mutations in *BRAF*^{V600}/*NRAS*$^{Q61R/K/L}$ wild-type (wt) melanoma. MEK-inhibitor monotherapy has activity in *BRAF*^{V600}/*NRAS*$^{Q61R/K/L}$ wt melanoma, but is associated with considerate skin toxicity. Skin toxicity associated with the MEK-inhibitor trametinib (T) can be effectively mitigated by adding a low dose (50 mg BID) of the BRAF-inhibitor dabrafenib (LD-D) (Awada et al. Ann Oncol 2020). **Methods:** This two-stage, single-center phase 2 trial investigated T 2 mg QD in patients (pts) with advanced *BRAF*^{V600}/*NRAS*$^{Q61R/K/L}$ wt melanoma who previously progressed on treatment with checkpoint inhibitors. In case of dose-limiting T-related skin toxicity, LD-D (50 mg BID) was added to T (pre-amend). The trial was amended in June 2019 to administer T upfront with LD-D (post-amend). Objective response rate (ORR, by RECIST v1.1) served as the primary endpoint. A Simon's two-stage optimal design was used (p_0 0.10; p_1 0.30; alpha 0.05; power 0.80): in case of $>$ 1 OR in the first 10 pts, 19 additional pts would be included in stage 2. The trial is considered positive if $>$ 5 OR are observed. **Results:** As of February 9, 2021, 16 pts (3 pre-amend; 13 post-amend) were included (median age 56.5; male 56.3%; stage IIIB 6.3%, IV-M1a-c 68.8%, IV-M1d 25.0%; ECOG performance status 0-1 93.8%; normal lactate dehydrogenase 56.3%). Median duration of follow-up is 17.9 weeks (wks; range 1.9-90.1). The ORR in 14 evaluable pts is 42.9% (5 confirmed and 1 unconfirmed partial response), the disease control rate is 71.4%. Four OR are ongoing after a median follow-up of 8.0 wks (range 0.0-77.0), 2 responding pts progressed on therapy after respectively 16.6 and 24.0 wks. Four out of 6 OR are observed in pts with MAPK-pathway activating mutations (3 class II *BRAF* and 1 *GNAQ* mutation). Eight pts (50.0%) have progressed (median progression-free survival 16.4 wks [95% confidence interval [CI] 6.9-25.9]); 4 pts (25.0%) have died (median overall survival 54.7 wks [95% CI 37.6-71.8]). Adverse events (AE) are observed in all pts (grade [G] 3-4 9 [56.3%]). Two pre-amend pts added on LD-D due to dose-limiting T-related skin toxicity; no clinically relevant T-related skin toxicity was observed post-amend with the upfront addition of LD-D. The most frequent AE were creatine kinase increase (G1-2 11 [68.8%]; G3-4 1 [6.3%]), and anemia and acneiform rash (both G1-2 7 [43.8%]; G3-4 0). Therapy was temporarily interrupted due to AE in 11 pts (68.8%) and permanently interrupted in 1 pt (6.3%) due to recurrent pneumonitis. **Conclusions:** In this two-stage phase 2 trial, T plus LD-D was found to have promising antitumor activity and acceptable toxicity in pts with advanced pretreated *BRAF*^{V600}/*NRAS*$^{Q61R/K/L}$ wt melanoma, especially in the presence of identifiable somatic MAPK-pathway activating mutations. Clinical trial information: NCT04059224. Research Sponsor: Stichting tegen Kanker, Pharmaceutical/Biotech Company.

9530 **Poster Session**

Discrepancies in response and immune-related adverse events (irAE) of anti-PD-1 monotherapy between races and primary sites in patients (pts) with advanced nonacral cutaneous melanoma (NACM).

Xue Bai, Alexander Noor Shoushtari, Allison Betof Warner, Henry Quach, Christopher G Cann, Michael Zhang, Lalit Pallan, Catriona Harvey, Lu Si, Bixia Tang, Chuanliang Cui, Michelle S. Kim, Tatyana Sharova, Keith Flaherty, Georgina V. Long, Alexander M. Menzies, Ryan J. Sullivan, Genevieve Marie Boland, Douglas Buckner Johnson, Jun Guo, MGH Melanoma Clinical Research Team; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Memorial Sloan Kettering Cancer Center, New York, NY; Vanderbilt University Medical Center, Nashville, TN; Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; Melanoma Institute Australia, Sydney, NSW, Australia; Royal North Shore Hospital, Sydney, Australia; MGH, Boston, MA; Massachusetts General Hospital Cancer Center, Surgical Oncology, Boston, MA; Dana-Farber Cancer Institute/Harvard Medical School/Massachusetts General Hospital, Boston, MA; Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Massachusetts General Hospital, Boston, MA

Background: Ultraviolet (UV)-induced high tumor mutation burden (TMB) of NACM is associated with response to anti-PD-1 monotherapy (aPD-1). Anatomic location of the primary lesion (reflecting UV exposure) and race (reflecting eumelanin level) may serve as surrogates for TMB and be associated with varying response and irAE patterns. **Methods:** Pts with advanced NACM receiving aPD-1 between 2009-2019 were retrospectively analyzed from 5 institutions in the US, Australia and China. Best response, survival (PFS and OS), and organ/system-specific irAEs were compared by race (Caucasian [C] vs non-Caucasian [NC]) and primary anatomic site. **Results:** Among 697 patients, 616 were C, 81 were NC. Complete response rate (CRR) was 24.8% (95%CI, 21.4-28.4) and 2.6% (95%CI, 0.3-9.1) and ORR was 54.9% (95%CI, 50.9-58.9) and 15.6% (95%CI, 8.3-25.6) in C and NC, respectively (both P<.001). Median PFS was 16.5 (95%CI, 12.0-23.1) and 5.2 (95%CI, 3.6-7.6) months, median OS was 60.5 (95%CI, 49.9-not reached [NR]) and 29.2 (95%CI, 17.9-NR) months, in C and NC, respectively (P<.001 and =.04). In multivariate analyses, C had significantly higher CRR (OR 13.4, 95%CI 3.1-57.4), ORR (OR 10.6, 95%CI 4.6-24.5), and longer PFS (HR 0.5, 95%CI 0.4-0.7) than NC. Compared to a head primary site, NACM from less UV-exposed regions had significantly lower CRR (upper trunk, OR 0.6, 95%CI 0.4-0.96; lower limb, OR 0.5, 95%CI 0.2-0.9), ORR (lower limb, OR 0.6, 95%CI 0.3-0.9) and poorer PFS (perineum/buttock, HR 2.1, 95%CI 1.2-3.5; lower limb, HR 1.6, 95%CI 1.2-2.2) and OS (perineum/buttock, HR 3.8, 95%CI 2.2-6.8; lower limb, HR 1.7, 95%CI 1.2-2.4). Overall irAE incidence was similar between C and NC but irAE subtypes varied. C had significantly higher incidence of GI (12.2%, 95%CI 9.5-15.3% vs 1.2%, 95%CI, 0.03-6.7%, P=.001), respiratory (10.3%, 95%CI 7.8-13.2% vs 0, P<.001) and grade 3/4 (15.4%, 95%CI 12.4-18.8% vs 6.2%, 95%CI 2.0-13.8%, P=.03) irAEs; and lower incidence of endocrine (13.8%, 95%CI 10.9-17.0% vs 32.1%, 95%CI 22.2-43.4%, P<.001) and liver (4.8%, 95%CI 3.2-7.1% vs 13.6%, 95%CI, 7.0-23.0%, P=.005) irAEs. IrAEs did not vary by primary NACM site. **Conclusions:** Race and primary site are independently correlated with distinct response and survival outcomes in pts with advanced NACM receiving aPD-1. IrAE subtypes vary by race although overall irAE incidence does not. Research Sponsor: None.

9531 **Poster Session**

Characterization of cytokine release syndrome (CRS) following treatment with tebentafusp in patients (pts) with previously treated (2L+) metastatic uveal melanoma (mUM).

Richard D. Carvajal, Takami Sato, Marcus O. Butler, Joseph J. Sacco, Alexander Noor Shoushtari, Jessica Cecile Hassel, Alexandra Ikeguchi, Leonel Fernando Hernandez-Aya, Matthew Rioth, Omid Hamid, Josep M. Piulats, Jason J. Luke, Douglas Buckner Johnson, Serge Leyvraz, Enrique Espinosa, Laura Collins, Michelle L. McCully, Sarah Lockwood, Shaad Essa Abdullah, Paul Nathan; Department of Medicine, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY; Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Clatterbridge Cancer Centre, Merseyside, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; University of Oklahoma Medical Center, Oklahoma City, OK; University of Michigain Health System, Ann Arbor, MI; University of Colorado Cancer Center, Aurora, CO; The Angeles Clinic and Research Institute, Los Angeles, CA; Instituto Català de Oncologia, Hospital Duran i Reynals, L'Hospitalet de Llobregat, Hospitalet De Llobregat, Spain; University of Pittsburgh, Pittsburgh, PA; Vanderbilt University Medical Center, Nashville, TN; Charite-Universitätsmedizin Berlin, Berlin, Germany; Department of Medical Oncology, La Paz University Hospital, Madrid, Spain; Immunocore, Abingdon, United Kingdom; Immunocore Ltd, Abingdon, United Kingdom; Pivotal Statistics Ltd, Macclesfield, United Kingdom; Mount Vernon Cancer Centre, London, United Kingdom

Background: Cytokine-mediated adverse events (AEs) are commonly reported in pts treated with T cell engaging therapies. Tebentafusp (tebe), a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells, has shown an overall survival benefit for pts with untreated mUM in a Ph3 trial (NCT03070392). Here we reviewed the incidence, kinetics, and outcome of CRS in tebe-treated pts on the IMCgp100-102 trial of 2L+ pts with mUM (NCT02570308). **Methods:** 127 HLA-A*02:01+ 2L+ mUM pts were treated with tebe at the RP2D of 68mcg following intra-patient dose escalation of 20 mcg dose 1 and 30 mcg dose 2. Pts were monitored overnight to allow management of hypotension and other cytokine-related AEs. Because the rate of severe CRS was low in Ph1, prophylactic corticosteroids, antihistamines or acetaminophen were not mandated. CRS was evaluated post-hoc according to ASTCT Consensus Grading criteria [1]. Circulating cytokines in serum were measured before and at 8hr and 12-24hr after dosing for the 1st, 3rd and 4th doses (n=105). This analysis was conducted on the primary analysis snapshot dated 04Jun20. **Results:** The most frequent treatment-related AEs that were likely cytokine-mediated included fever (80%), chills (64%), nausea (59%), hypotension (41%) and hypoxia (4%). In a post-hoc review using ASTCT criteria, 86% of pts (n=109) had any grade CRS. The majority of these 109 pts had either grade (G) 1 (n=42; 33%) or G2 (n=62; 49%), with few G3 (n=4; 3.1%), one G4 (0.8%), and no deaths. Onset of CRS began within 24 hours of administration and G≥2 hypotension or hypoxia typically resolved within 2 days of onset. Most CRS events occurred after the first 3 doses with a marked reduction in the frequency and severity of CRS thereafter; G3-4 CRS was limited to first two doses. Only 2 pts discontinued tebe due to CRS (1 G3 and 1 G4). Treatment of G≥2 CRS included iv fluids (n=45), iv steroids (n=18), oxygen (n=8), and vasopressor use (n=2). No pts received tocilizumab. Tebe induced a transient increase in peripheral cytokines, including IFNγ, IL-10, IL-6 and TNFα, within hours of tebe dosing, which were several fold higher in pts with CRS compared to pts without CRS. Higher levels of TNFα trended with severity of CRS. **Conclusions:** CRS, a common AE observed with all T cell engaging therapies, was frequently observed within 24 hours of initial tebe treatment. Most CRS events were mild or moderate in severity even without the use of prophylactic premedications, were reversible with standard management strategies, decreased in frequency and severity with subsequent doses, and rarely led to treatment discontinuation. Pts with CRS tended to have greater increases in serum cytokines, consistent with tebe's proposed mechanism of action. [1] Lee, DW et al. *Biol Blood Marrow Transplant* 2019. Clinical trial information: NCT02570308. Research Sponsor: Immunocore.

9532 **Poster Session**

Triplet therapy with pembrolizumab (PEM), encorafenib (ENC) and binimetinib (BIN) in advanced, BRAF V600 mutant melanoma: Final results from the dose-finding phase I part of the IMMU-Target trial.

Lisa Zimmer, Angela Krackhardt, Erwin S. Schultz, Daniela Goeppner, Chalid Assaf, Dietrich Trebing, Elisabeth Livingstone, Dirk Schadendorf; Department of Dermatology, University Hospital, University Duisburg-Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany; Technische Universität MüNchen, School of Medicine, Klinik Und Poliklinik Für Innere Medizin III, Klinikum Rechts Der Isar, German Cancer Consortium (DKTK), Technische Universität München, Partner Site Munich, Munich, Germany; Department of Dermatology, University Hospital of the Paracelsus Medical Private University, Nuremberg, Germany; Department of Dermatology, Justus-Liebig-University, Giessen, Germany; Department of Dermatology, Helios-Klinikum Krefeld, Krefeld, Germany; Department of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane, Dessau, Germany; Department of Dermatology, University Hospital Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany; Department of Dermatology, University of Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany

Background: Survival of BRAF-mutated melanoma profoundly improved since the introduction of immune checkpoint inhibitors (ICI) and MAPK pathway inhibitors (MAPKi). Response kinetics of ICI and MAPKi are complementary, mechanistic evidence indicates that MAPKi may affect the tumor immune microenvironment. Combined use of both drug classes may further enhance clinical benefit. IMMU-Target was set-up as a prospective, open-label, phase I/II trial, with a safety phase I part followed by a randomized phase II part, to study the tolerability and clinical activity of PEM, ENC and BIN triplet therapy. **Methods:** Treatment naïve adult patients (pts) with stage IIIB-IV (AJCC 2017), BRAF V600 mutant melanoma with measurable disease but no active brain metastasis were eligible. The dose finding part used a 3+3 design, starting with a dose level (DL) 0 applying the clinically recommended doses of PEM (200 mg Q3W), ENC (450 mg QD) and BIN (45 mg BID). In case of ≥2 dose-limiting toxicities (DLT), a reduction of the ENC and BIN doses (300 mg QD and 30 mg BID at DL-1, 200 mg QD and 30 mg BID at DL -2) was foreseen. Primary endpoints of the phase I part were safety and tolerability. **Results:** From April 2018 until May 2020, 14 pts with BRAF V600 mutations were enrolled. 2 of 3 pts at DL 0 developed DLT (creatine phosphokinase (CPK) elevations grade 3 plus cytokine release syndrome grade 4; gamma glutamyl transferase (GGT) elevations grade 3), and had to stop therapy early. Therefore, 3+3 further pts at DL -1 were included with no DLT observed in these 6 pts. One (isolated GGT elevations grade 3) of the 2 DLT observed in the 3 pts of DL 0 enrolled initially was questionable as DLT, as the patient had further episodes of isolated GGT elevations without therapy. As a result, further 5 pts were enrolled at DL 0: here no DLT-matching treatment-related adverse event (TRAE) occurred. In total, 12 out of 14 pts (86%) experienced a TRAE and 7 (50%) experienced a grade ≥3 TRAE; there were no fatal AE or TRAE-related deaths. Increases in alanine and in aspartate aminotransferases, GGT and CPK elevations (6 of 14 pts) were the most common grade 3-4 TRAE. In median, pts at DL 0 (n=8) received triplet therapy for 18 weeks (IQR 7.5-29), at DL-1 (n=6) for 46 weeks (IQR 27-102). The overall response rate was 64% (95% CI=35-87). At a median follow-up of 10.0 months at DL 0 and 27.0 months at DL-1, progression-free survival at 12 months was 37.5% (95% CI 9- 67) and 60% (95% CI 13-88), respectively. **Conclusions:** Triplet therapy was feasible and safe at both dose levels leading to clinically meaningful disease control. The phase II part was not initiated, since the clinical efficacy of PEM plus ENC and BIN is currently investigated in STARBOARD (NCT04657991), a prospective, randomized, placebo-controlled (PEM mono), double-blinded phase III trial. Clinical trial information: NCT02902042. Research Sponsor: Funding in part by Merck Sharp & Dohme and Array/Pfizer.

9533 **Poster Session**

Patterns and management of progression on first-line ipilimumab combined with anti-PD-1 (IPI+PD1) in metastatic melanoma (MM) patients.

Ines Pires Da Silva, Judith M. Versluis, Tasnia Ahmed, Douglas Buckner Johnson, Jennifer Soon, Clara Allayous, Camille Lea Gerard, Joanna Mangana, Oliver Klein, Lisa Zimmer, Caroline Robert, Maria Grazia Vitale, Hui-Ling Yeoh, Olivier Michielin, Celeste Lebbe, Shahneen Kaur Sandhu, Christian U. Blank, Matteo S. Carlino, Alexander M. Menzies, Georgina V. Long; Melanoma Institute Australia, Sydney, Australia; Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Melanoma Institute Australia, Sydney, NSW, Australia; Vanderbilt University Medical Center, Nashville, TN; Peter MacCallum Cancer Centre, Melbourne, Australia; APHP Department of Dermatology, Paris University Saint-Louis Hospital, U976 Paris, Paris, France; Center of Personalized Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland; University Hospital Zürich, Zürich, Switzerland; Medical Oncology Unit, Austin Health, Heidelberg, Australia; Department of Dermatology, University Hospital, University Duisburg-Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany; Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France; Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori-IRCCS Fondazione "G. Pascale", Naples, Italy; Alfred Health, Melbourne, NSW, Australia; Center of Personalized Oncology, Lausanne University Hospital (CHUV), Switzerland, Molecular Modeling Group, Swiss Institute of Bioinformatics, Lausanne, Switzerland; APHP Dermatology and CIC, U976, Université de Paris, Hôpital Saint-Louis, Paris, France; Peter MacCallum Cancer Center, Melbourne, VIC, Australia; Westmead Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Background: First line IPI+PD1 induces long-term response in 36% of MM patients (pts); however, the majority of pts will progress and may require further treatment, which is yet to be established. We studied the patterns of progressive disease (PD) on 1st line IPI+PD1, and the management and outcomes in MM pts. **Methods:** Demographics, disease characteristics, nature of PD, subsequent treatments and outcomes were examined in MM pts with PD on 1st line IPI+PD1. Multivariable analyses (MVA) identified factors associated with patterns of PD: innate resistance (IR) = PD as best response or stable disease (SD) $<$ 6 mo; acquired resistance (AR) = PD after initial response or SD $\geq$ 6 mo. **Results:** 310 MM pts from 14 melanoma centres were included; 208 (67%) had PD during and 102 (33%) after ceasing IPI+PD1. Overall med. progression-free survival (mPFS) was 2.8 mo (CI 95% 2.7 – 3.0); 187 pts (60%) had IR (mPFS 2.2 [2.1 – 2.5]), 112 pts (36%) had AR (mPFS 8.5 [7.2 – 10.2]) and 11 pts (4%) had pseudoprogression, i.e. PD followed by response without changing treatment (mPFS 2.7 mo [1.4 – NA]). On MVA, pts with ECOG PS $\geq$ 1 were more likely to have IR vs AR; and within IR pts, those with head & neck primary melanomas and lung metastases were more likely to have PD $<$ 1.5 mo. Most pts with IR (68%) had PD in multiple sites, while 61% AR pts had PD in a single site. Brain was most common site of single organ PD; 49% of IR and 41% of AR. Med. follow-up from PD was 32.7 mo (28.1 – 36.8). After PD, 61 pts (20%) had best supportive care (26% of IR and 11% of AR pts). 259 pts (80%) received further treatment: 39% IR pts had systemic treatment (ST) only and 27% had ST + local; 31% AR pts had ST only and 39% had ST + local. Of 200 pts (65%) who had ST(+/-local), 54% had 1 line of ST and 46% had $\geq$ 2; 1st line ST (ST1) was BRAF/MEKi in 36% of pts, PD1 in 32%, IPI+PD1 in 7%, investigational drugs in 11%, chemotherapy in 9% and others in 5%. ORR in IR pts was lower than in AR pts for every type of ST1 (see Table). Med. OS from PD was 11.4 mo (CI 95% 9.6 – 16.1); IR 6.4 mo (CI 95% 5.6 – 10.2) and AR 26.1 mo (CI 95% 17.1 – NA). **Conclusions:** These data suggest longer OS from PD for AR vs IR pts independent of ST type. BRAF/MEKi, rechallenge with PD1+/-IPI and investigational drugs showed activity after PD on IPI+PD1, while chemotherapy has no role in this context. Research Sponsor: None.

ST after PD on IPI+PD1	BRAF/MEKi	PD1	IPI+PD1	Investigational drugs	Chemotherapy
ORR 1st line, n/N (%)					
IR	30/51 (59)	7/27 (26)	1/5 (20)	1/15 (7)	0/15 (0)
AR	13/20 (65)	11/36 (31)	3/9 (33)	1/6 (17)	0/3 (0)
Total	43/71 (61)	18/63 (29)	4/14 (29)	2/21 (10)	0/18 (0)
ORR any line, n/N (%)	61/102 (60)	26/79 (33)	9/36 (25)	7/47 (15)	1/42 (2)
Disease control rate 1st line, n/N (%)	53/71 (75)	35/63 (56)	6/14 (43)	7/21 (33)	0/18 (0)
mPFS 1st line, mo (95% CI)	8.9 (6.0-15.4)	5.0 (3.6-12.6)	7.5 (2.7-NA)	2.9 (2.0-4.9)	1.7 (1.3-2.2)
12-mo PFS rate (%)	42	37	35	6	6
mOS 1st line, mo (95% CI)	18.9 (12.4-30.0)	32.6 (18.7-NA)	15.6 (10.5-NA)	17.7 (16.1-NA)	4.4 (3.2-13.5)

9534 **Poster Session**

Characteristics and probability of survival for patients with advanced melanoma who live five or more years after initial treatment with immune checkpoint blockade (ICB).

Kimberly Loo, Debra A. Goldman, Katherine Panageas, Margaret K. Callahan, Paul B. Chapman, Parisa Momtaz, Alexander Noor Shoushtari, Jedd D. Wolchok, Michael A. Postow, Allison Betof Warner; Memorial Sloan Kettering Cancer Center, New York, NY; Medical Oncology, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, NY

Background: A subset of melanoma patients treated with ICB (ipilimumab [ipi], nivolumab [nivo], pembrolizumab [pembro] or nivo+ipi) will experience durable responses. While five-year survival rates have been reported for patients treated with ICB on clinical trials, little is known about the clinical characteristics, survival past five years, and patterns of late relapse of long-term survivors. **Methods:** We retrospectively reviewed all patients treated at Memorial Sloan Kettering for unresectable stage III/IV melanoma who survived at least five years following their first dose of ICB (N = 151). Demographics, disease characteristics, and nature of progression were examined. Overall survival (OS) was calculated from 5 years post-ICB. Time to Treatment failure (TTF) was calculated conditionally from 5 years out until next therapy, progression, or death. **Results:** Of the 151 long-term survivors, median age at first ICB treatment was 62 years (range 22-83), with 101 (66.9%) male and 50 (33.1%) female patients. Stage at first ICB treatment was unresectable stage III (26, 17.2%), M1a (21,13.9%), M1b (39, 25.8%), M1c (52, 34.4%), M1d (13, 8.6%). Melanoma subtype was cutaneous (122, 80.8%), unknown primary (24, 15.9%), mucosal (3, 2%), and acral (2, 1.3%). First ICB was ipi (108, 71.5%), PD-1 (nivo or pembro) (5, 3.3%), and nivo+ipi (37, 24.5%). The best overall response to first ICB was CR (76, 50.3%), PR (27, 17.9%), SD (16, 10.6%) and PD (32, 21.2%). Of the patients who progressed after initial ICB, 38 received subsequent systemic treatment as follows: PD-(L)1 in 20 (53%), BRAF ± MEK in 9 (23.7%), ipi in 7 (18.4%), and chemotherapy in 2 (5.3%). Median duration of follow-up among survivors (N = 138) was 93 months (range 60-192). From 5 years post-ICB, 85% (95% CI: 73-92%) survived an additional 5 years. In those who made it to 5 years without treatment failure (N = 72), the probability of remaining failure-free was 92% (95% CI: 86-99%) at 7 years. Of the 151 patients, only 4 patients (2.6%) experienced disease progression after 5 years. Three patients had radiographic or pathologic disease progression in the lymph nodes and one in the subcutaneous tissue. No patients progressed in the lungs, visceral organs, or CNS after 5 years. At time of analysis, 13 (8.6%) patients died after 5 years post ICB, none died of progressive melanoma. 6 patients died of unknown causes, 2 died of other causes, and 5 died of other non-melanoma cancer-related causes. **Conclusions:** Patients who survive five years after their initial immunotherapy have excellent overall survival and treatment failure-free survival. Given the anxiety surrounding survivorship and late progression, long-term survivors should be reassured of their excellent prognosis. These data suggest that aggressive follow-up schedules and imaging of melanoma patients after 5 years of survival may not be required. Research Sponsor: None.

9535 **Poster Session**

Clinical characteristics of SF3B1 mutant (mut) uveal melanoma (UM) and response to immune checkpoint inhibition (ICI).

Joe Grimes, Alexander Noor Shoushtari, Marlana Orloff, Shaheer Khan, Cody Chiuzan, Susan Jean Hsiao, Diana McDonnell, Brian P. Marr, Richard D. Carvajal; Columbia University Vagelos College of Physicians and Surgeons, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA; Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY; Columbia University Irving Medical Center, New York, NY; New York Presbyterian Hospital/Columbia University Medical Center, New York, NY; Columbia University School of Nursing, New York, NY; Columbia University Medical Center, New York, NY

Background: Metastatic UM is associated with a median overall survival (OS) $<$ 1 year (yr) and overall response rate (RR) to ICI $<$ 18%. SF3B1 mut UM represent a clinically unique subset of UM, distinct from BAP1 mut disease, characterized by aberrant spliceosome machinery which may result in increased neoantigen presentation, increased immunogenicity, and sensitivity to ICI. To assess these hypotheses, we performed a multicenter retrospective analysis to assess the natural history and response to ICI in patients (pts) with SF3B1 mut UM. **Methods:** Patients were identified from institutional databases and the AACR Project GENIE Consortium. Data collected included: baseline and recurrent disease characteristics, molecular characteristics, treatments received, treatment response, and vital status. Efficacy endpoints included investigator assessed RECIST RR and OS. **Results:** 58 pts with deleterious SF3B1 mutations were identified: 56 R625; 1 D781G; 1 G742D. Median age at diagnosis (dx) was 52 (range, 14-87). 50% were female. 49 pts developed distant metastases. The median time from initial dx to metastasis was 6.1 years (yrs; range, 0.9 to 26.7). Initial metastatic sites (n = 48) were: liver-only (52%); non-liver-only (29%); mixed liver and non-liver disease (19%). The most common initial metastatic sites were: liver (71%), lung (29%), soft tissue (13%), lymph node (8%), and bone (4%). The median OS for all pts from time of metastasis was 3.9 years (95% confidence interval (CI), 2.3-6.2) with OS for pts with non-liver only disease at 6.2 yrs vs those with liver-only or mixed disease at 3.4 yrs (hazard ratio = 2.12, p = 0.14). 1-year OS rate from time of metastasis was 94% (95% CI, 0.86-0.99). 34 pts received ICI for metastatic disease at which time 27% had received a prior systemic therapy (median, 0; range, 0-3) and 35% had received a prior hepatic regional therapy (median, 0; range, 0-6). 15 pts received single-agent anti-PD1; 4 received ipilimumab alone; 15 received dual ICI. 10 pts received ICI with concurrent hepatic regional tx. Best response among 33 evaluable pts were: 9% partial response; 39% stable disease; 52% progressive disease. Median OS from ICI initiation was 20.2 months (95% CI, 13.1-27.4). 1-year OS from ICI initiation was 74% (95% CI, 0.59-0.90). **Conclusions:** SF3B1 mut UM is characterized by later development of metastases, more common involvement of extrahepatic sites, and longer OS when compared with historical datasets of molecularly unselected UM. Although a modest RR to ICI was observed, the median OS and 1-year survival rate post-ICI are numerically superior to historical controls. Given the more indolent course of SF3B1 mut UM, stratification by SF3B1 status should be included in future clinical trials. Research Sponsor: None.

9536 **Poster Session**

Pembrolizumab and all-trans retinoic acid combination treatment of advanced melanoma.

Martin McCarter, Richard P. Tobin, Dasha T. Cogswell, Victoria M. Vorwald, Dana Davis, Robert J. Van Gulick, Kasey L. Couts, Kimberly R. Jordan, Victoria Nuanes, Dexiang Gao, Theresa Michelle Medina, Karl D. Lewis, Rene Gonzalez, Ross W. McFarland, William A. Robinson; University of Colorado Comprehensive Cancer Center, Aurora, CO; University of Colorado Anschutz Medical Campus, Aurora, CO; Univeristy of Colorado Anschutz Medical Campus, Aurora, CO; University of Colorado, Aurora, CO; Division of Medical Oncology, University of Colorado Cancer Center, Aurora, CO; Front Range Cancer Spclsts, Fort Collins, CO

Background: Myeloid-derived suppressor cells (MDSCs) are potent suppressors of antitumor immunity and are commonly associated with poor outcomes in melanoma patients treated with immune checkpoint inhibitors. Inducing the differentiation of MDSCs using all-trans retinoic acid (ATRA) reduces MDSC frequency. This analysis seeks to assess the safety and efficacy of combining ATRA and pembrolizumab in advanced melanoma patients. **Methods:** This single arm, single institution, phase I/II study (NCT03200847) enrolled 24 patients diagnosed with stage IV melanoma. Eligible patients were over the age of 18 and had not been previously treated anti-PD-1 therapy. Treatment consisted of 200mg Q3W pembrolizumab plus the supplemental treatment of 150 mg/m2 ATRA orally for 3 days surrounding each of the first four infusions of pembrolizumab, with patients continuing pembrolizumab for up to two years until confirmed disease progression or unacceptable toxicity. The primary endpoints were safety and reduction in circulating MDSCs. Secondary endpoints were overall response rate (ORR), disease control rate (DCR), progression free survival (PFS) according to RECIST v1.1. **Results:** At data cut off (Feb, 2021) 22 patients were evaluable for tumor response. Median follow-up was 1.0 years (0.3-2 years). In general, the combination of pembrolizumab and ATRA was well tolerated. The most common treatment-related adverse events (AEs) were grade 1 or 2, including headache (22 pts, 92%), fatigue (18 pts, 75%), rash (16 pts, 66%), and nausea (8 pts, 33%), most of which corresponded with the 3-day course of ATRA treatment. Ten patients had grade 3 or higher AEs with most being common ICI-related AEs. The ORR was 60% and DCR was 83%. Six-month PFS rate was 62%. Excluding patients diagnosed with uveal melanoma (n = 2) the ORR was 72%, DCR was 86%, and the six-month PFS rate was 68%. Paired analysis showed sustained decreases in absolute numbers ($p = 0.002$) and percentage ($p = 0.007$) of circulating MDSCs ($CD3^{-}CD19^{-}CD56^{-}CD11b^{+}CD33^{+}HLA\text{-}DR^{-/low}$) 4-6 weeks after stopping ATRA. The study is ongoing and further data will be presented in the future. **Conclusions:** This study demonstrates that the combination of ATRA and pembrolizumab is well tolerated and suggests that reducing MDSCs with ATRA may enhance the efficacy of pembrolizumab. This strategy of targeting MDSCs in combination with pembrolizumab warrants further development. Research Funding: Merck. Clinical trial information: NCT03200847. Research Sponsor: Merck Sharp & Dohme Corp.

9537 **Poster Session**

Safety and efficacy of lifileucel (LN-144), an autologous, tumor infiltrating lymphocyte cell therapy in combination with pembrolizumab for immune checkpoint inhibitor naïve patients with advanced melanoma.

Sajeve Samuel Thomas, Gino Kim In, Bernard Doger, Simon Haefliger, Juan Martin-Liberal, Zelanna Goldberg, Alex Cacovean, Rana Fiaz, Guang Chen, Madan H. Jagasia, Friedrich Graf Finckenstein, Maria Fardis, Antonio Jimeno; University of Florida Health Cancer Center at Orlando Health, Orlando, FL; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Hospital Universitario Fundacion Jimenez Diaz - START Madrid, Madrid, Spain; Inselspital Universitätsspital Bern, Bern, Switzerland; ICO Hospitalet, Hospital Duran i Reynals, Barcelona, Spain; Iovance Biotherapeutics, Inc., San Carlos, CA; University of Colorado Comprehensive Cancer Center, Aurora, CO

Background: Tumor infiltrating lymphocyte (TIL) cell therapy has demonstrated safety and efficacy in advanced melanoma, both in the pre-immune checkpoint inhibitor (ICI) setting (Goff, JCO 2016) and in patients who have failed anti-PD-1/PD-L1 therapy (Sarnaik, 2020). Combination of TIL and pembrolizumab (pembro) in ICI-naïve patients has demonstrated encouraging efficacy data with acceptable safety in head and neck squamous cell carcinoma (Jimeno, 2020). To improve treatment options in early lines, we explore a combination of LN-144 and pembro in patients with ICI-naïve advanced melanoma. **Methods:** IOV-COM-202 is a Phase 2 multicenter, multi-cohort, open-label study evaluating TIL cell therapy in multiple settings and indications. We report on Cohort 1A enrolling ICI-naïve advanced melanoma (unresectable or metastatic) patients for treatment with a combination of LN-144 and pembro. Key eligibility criteria include $\leq$ 3 lines of prior therapy, ECOG $<$ 2, one resectable lesion for lifileucel manufacturing, and $\geq$ 1 measurable lesion for response assessment. Primary endpoints are objective response rate (ORR) per RECIST 1.1 and safety as measured by incidence of Grade $\geq$3 treatment-emergent adverse events (TEAE). LN-144 is generated at centralized GMP facilities in a 22-day process. A nonmyeloablative lymphodepletion (NMA-LD) using cyclophosphamide and fludarabine is administered preceding a single LN-144 infusion, followed by $<$ 6 doses of IL-2 (600,000 IU/kg). Pembro is administered after tumor harvest but prior to NMA-LD and continues after lifileucel per label. **Results:** Seven patients have received lifileucel in combination with pembro as of data extraction date (Feb 14, 2021). Five of the 7 treated patients were treatment-naïve, 1 patient had prior BRAFi + MEKi and 1 had received prior chemotherapy; 71% had liver/brain lesions, 43% had LDH $>$ ULN. Mean SOD for the target lesions was 111 mm, with 86% of patients with $>$ 3 target lesions, representing advanced disease at baseline for this patient group. The TEAE profile was consistent with the underlying disease and known AE profiles of pembro, NMA-LD and IL-2. Six patients had a confirmed objective response with an ORR of 86% (1 CR, 5 PR) and 1 best response of SD. Three of the responding patients have remained off pembro due to pembro related AEs for 3, 4 and 13 months (mos), yet maintaining response. All responding patients remain in response with the longest duration of response being 16.8 mos. **Conclusions:** Lifileucel can be safely combined with pembro in patients with ICI-naïve advanced melanoma. The ORR of 86% is encouraging when compared to pembro alone in a similar patient population, especially considering the disease burden at baseline and persistence of responses in patients off therapy. Enrollment is ongoing and updated data to be presented. Clinical trial information: NCT03645928. Research Sponsor: Iovance Biotherapeutics, Inc.

9538 **Poster Session**

The use of cryoablation to overcome resistance to PD-1 blockade in unresectable melanoma.

Meghan Mooradian, Florian J. Fintelmann, Howard E. Kaufman, Mari Mino-Kenudson, Jaimie Lynn Barth, Aleigha Lawless, Tatyana Sharova, Riley Fadden, Krista M. Rubin, Donald P. Lawrence, Dennie T. Frederick, Moshe Sade-Feldman, Ryan J. Sullivan; Massachusetts General Hospital Cancer Center, Boston, MA; Massachusetts General Hospital, Boston, MA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Massachusetts General Hospital Cancer Center, Surgical Oncology, Boston, MA; Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA

Background: Percutaneous image-guided cryoablation (cryo) is an established minimally invasive oncologic treatment that modulates the immune microenvironment. We hypothesized that cryo can augment anti-tumor responses in melanoma patients progressing on immune checkpoint inhibitors (ICI). **Methods:** In this non-randomized phase II single-center study, subjects with unresectable melanoma progressing on ICI underwent cryo of an enlarging lesion and ICI continuation for a minimum of 2 additional cycles. Computed tomography was performed at 6-8 weeks following cryo to determine tumor response in non-ablated lesions per RECIST1.1, with confirmatory scans at 8-12 weeks. The primary endpoint was safety and feasibility. Secondary endpoints were overall response rate (ORR) and disease control rate (DCR) with DCR defined as the percentage of pts who achieve complete response (CR), partial response (PR), and stable disease (SD). Correlative analyses on pre- and post-cryo tumor biopsy and blood samples were performed. **Results:** From May 2018 through July 2020, 20 pts were screened, 18 enrolled and 17 treated per protocol. All pts received prior PD-1/PD-L1 monotherapy and 12 (67%) experienced primary resistance to ICI. Median follow-up was 8.5 months. Ablated lesions included lymph nodes (n = 4), lung/pleura (n = 4), soft tissue/bone (n = 3), adrenal (n = 3), chest wall (n = 1), and kidney (n = 1). Peri-procedural events occurred in 3 cases (pneumothorax, diaphragm puncture, osteomyelitis). One pt. with underlying ICI-induced hypophysitis experienced an adrenal crisis post-procedure, which rapidly corrected with stress-dose steroid administration; there were no de novo immune-related adverse events post-ablation and there were no grade 4/5 events. In evaluable pts (n = 17), ORR was 18% and DCR was 47% (3 PR, 5 SD). To investigate the inflammatory state of the tumor microenvironment prior to cryo, PD-1, CD8+ TIL IHC, was performed and will be presented at the meeting. Additional exploratory analyses (serial ctDNA analysis, single cell RNA sequencing, HLA-subtyping) are ongoing. **Conclusions:** Cryoablation in patients with unresectable melanoma following progression on ICI is feasible with an acceptable side effect profile. Efficacy data of this potentially synergistic approach in metastatic melanoma is encouraging. Correlative analyses are underway to identify biomarkers of response to this novel strategy. Clinical trial information: NCT03290677. Research Sponsor: Philanthropy - donations to the MGH melanoma group.

Characteristic	Patients (n = 18)
Median age (years)	63.5 (47-90)
ECOG Status, n (%)	
0-1	14 (78)
2	4 (22)
Line of therapy, n (%)	
1st	8 (45)
2nd	6 (33)
3rd	4 (22)
Median duration of ICI prior to cryo (days)	103 days (41 – 1250)
Best response (RECIST 1.1)*, n (%)	
CR	0
PR	3 (18)
SD	5 (29)
PD	9 (53)
Pts remaining on post-cryo ICI and/or who completed planned ICI course, n (%)	3 (18)

*Out of 17pts; 1pt did not have subsequent ICI and lacks confirmatory imaging.

9539 **Poster Session**

Apatinib in combination with camrelizumab, a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1, in patients with metastatic acral melanoma.

Xuan Wang, Chuanliang Cui, Bin Lian, Lu Si, Zhihong Chi, Xinan Sheng, Yan Kong, Lili Mao, Xue Bai, Bixia Tang, Xieqiao Yan, Siming Li, Li Zhou, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: Patients(pts) with metastatic acral melanoma respond poorly to anti–PD-1 monotherapy. Apatinib, a vascular endothelial growth factor (VEGF) inhibitor, is a kind of anti-angiogenic drugs which have shown synergistic therapeutic effects in combination with PD-1 blockade. We conducted this single-center, open label phase trial to evaluate the safety and efficacy of camrelizumab in combination with apatinib in advanced treatment-naïve acral melanoma pts. **Methods:** Eligible participants were adult pts (aged 18 to 75) with histologically confirmed unresectable stage or distant metastatic acral melanoma. Exclusion criterion included unknown primary melanoma, brain metastatic disease or previous use of anti PD-1 ab. Pts received camrelizumab at 200mg intravenous infusion every 2 weeks, in combination with apatinib 250 mg orally once a day. The primary endpoint was ORR according to RECIST 1.1 criteria, and the secondary endpoints were safety and RFS. **Results:** Thirty pts were enrolled from April 2019 to January 2021. Basic characteristics: the mean age was 56.7 years, 22 pts were at stage, 33.3% had an elevated LDH level. Median tumor burden was 45mm (10-187). Gene mutation: Nras 4, cKit 3, Braf 2. Up to January 2021, 27 pts could be evaluated, in which 2 pts got CR, 4 pts achieved PR, and 63% experienced tumor shrinkage. The ORR and DCR were 22.2% and 77.8%, respectively. With a median follow up time of 8.3 months, the median PFS was 8.0 months (95% CI, 3.68, 10.19), the one-year durable response rate was 83.3% and the duration of response time was still not reached. Univariate analysis showed high LDH level was negatively associated with PFS. Whole exome data of baseline tumor biopsies revealed a positive correlation between high copy number variation (CNV) plus high mutational load (TMB) and efficacy , and all of the 4pts with MDC1 gene mutation got tumor shrink and 2 got PR. 96.7% pts experienced treatment-related AEs (TRAEs), including hand foot syndrome in 40%, proteinuria in 40%, liver dysfunction in 36.7%, and hypothyroidism in 30%. The grade 3-4 TRAEs were 33.3%. AE-related permanent discontinuation occurred in only 13.3% pts. 6 pts had delays of treatment due to the COVID-19 epidemic. No dose-limiting toxicities and suspected unexpected AEs were observed in the combination. **Conclusions:** The combination of apatinib plus camrelizumab was tolerable and showed promising antitumor activities and PFS improvement in pts with treatment-naïve metastatic acral melanoma. The survival is still in follow up. Clinical trial information: NCT03955354. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co.

9540 **Poster Session**

Predictors of overall survival (OS) in patients (pts) with melanoma brain metastasis (MBM) in the modern era.

Merve Hasanov, Denai R. Milton, Alicia Bea Davies, Elizabeth Sirmans, Chantal M Saberian, Eliza Posada, Jeffrey E. Gershenwald, Carlos A. Torres-Cabala, Jason T. Huse, Hussein Abdul-Hassan Tawbi, Isabella Claudia Glitza, Jing Li, Caroline Chung, Debra Yeboa, Sylvia Opusunju, Betty Y.S. Kim, Frederick F. Lang, Lauren Elaine Haydu, Michael A. Davies, Sherise D. Ferguson; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The management and OS of pts with metastatic melanoma have improved due to new systemic therapies. However, relatively little is known about the use of these treatments (tx) and their association with OS in pts with MBMs. We reviewed a large cohort of MBM pts to assess how pt demographics, disease characteristics, and MBM tx impact OS in the current era. **Methods:** Under an institutional review board-approved protocol, retrospective data were curated and analyzed from pts diagnosed with, and received tx for, MBM from 2014 to 2018 at the MD Anderson Cancer Center (MDA). Pts diagnosed with uveal or mucosal melanoma or other cancers were excluded. Pt demographics; timing and features of initial melanoma dx; timing and features of initial MBM dx; prior, initial and subsequent tx; and OS were collected. OS was determined from MBM dx to last clinical follow-up (FU). Pts alive at last FU were censored. The Kaplan-Meier method and log-rank test were used to estimate OS and to assess univariate group differences, respectively. Multivariable (MV) associations of OS with variables of interest were investigated with Cox proportional hazards models. Initial treatment of MBM was assessed as a time-varying covariate. All statistical tests used a significance level of 5%. **Results:** A total of 401 MBM pts were identified. The median age at MBM dx was 61; 67% were male and 46% had a BRAF V600 mutation. At MBM diagnosis dx, most (70%) pts were asymptomatic; 70% had concurrent uncontrolled extracranial disease; 36% had elevated serum LDH. Prior tx included immunotherapy (IMT) for 39% and targeted therapy (TTX) for 17%. The median number of MBMs was 2; 31% had $>$ 3 MBMs. Median largest MBM diameter was 1.0 cm, 9% had MBM $>$ 3.0 cm, and 5% had concurrent leptomeningeal disease (LMD). Tx received after MBM dx included stereotactic radiosurgery (SRS; 53% as initial tx for MBM, 67% at any time after MBM dx), whole brain radiation therapy (WBRT; 16%, 35%), craniotomy (12%, 19%), IMT (37%, 74%), and/or TTX (22%, 40%). 31% received steroids during initial MBM tx. At a median FU of 13.4 (0.0 - 82.8) months (mos), the median OS was 15.1 mos, and 1- and 2-year OS rates were 56% and 40%. Notably, gender, time to MBM dx, and BRAF status were not associated with OS (univariate analysis). On MV analysis, clinical features associated with worse OS included increased age, increased primary tumor thickness, elevated LDH, $>$ 3 MBMs, +LMD, +symptoms, and prior tx with IMT. Among tx used at any time after MBM dx, WBRT (HR 1.9, 95% CI 1.5-2.5) was associated with worse OS; SRS (HR 0.7, 95% CI 0.5-0.8) and IMT (HR 0.6, 95% CI 0.5-0.8) were associated with improved OS. **Conclusions:** In one of the largest cohorts of MBM pts described to date, OS has improved in MBM pts in the current era. Prognostic factors for OS include pt age, primary tumor and MBM features, prior tx, and tx for MBM. Additional analyses to assess the interaction of tx, disease features, and OS will be presented. Research Sponsor: None.

9541 **Poster Session**

KEYNOTE-555 Cohort B: Efficacy, safety, and PK of pembrolizumab (pembro) 400 mg every 6 weeks (Q6W) as 1L therapy for advanced melanoma.

Conrad R. Jacobs, Bernardo Leon Rapoport, Sze Wai Chan, Paul Ruff, Ana Maria Arance, Karmele Mujika, James Robert Anderson, Mallika Lala, Lokesh Jain, Omobolaji Oyekunle Akala, Elliot Chartash, Graham Lawrence Cohen; East Cape Onc, Cape Town, South Africa; The Medical Oncology Centre of Rosebank, Johannesburg, South Africa; Sandton Oncology Centre, Sandton, South Africa; University of Witwatersrand Faculty of Health Sciences, Johannesburg, South Africa; Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Hospital Oncologikoa, San Sebastian, Spain; Merck & Co., Inc., Kenilworth, NJ; Memor Sloan Kettering Cancer Center, New York, NY; Mary Potter Cancer Centre Pretoria, Johannesburg, South Africa

Background: In KEYNOTE-555, a model-based approach suggested expected drug exposure with pembro 400 mg Q6W is similar to that observed with approved doses of pembro 200 mg or 2 mg/kg Q3W. The pembro Q6W dose is now approved. We present interim efficacy, safety and PK of 1L pembro 400 mg Q6W for patients (pts) with advanced melanoma in KEYNOTE-555 Cohort B (NCT03665597). **Methods:** Eligible pts had unresectable stage III or IV melanoma, ECOG PS $\leq$1, and no prior systemic therapy for advanced disease.Pts received pembro 400 mg Q6W for up to 18 cycles ($\approx$2 years).The primary efficacy endpoint was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included PFS by BICR per RECIST v1.1 and safety. PK profile and exposure were evaluated for cycle 1 and steady state (cycle 4). **Results:** Between May 2019 and Jan 2020, 101 pts were enrolled and received $\geq$1 dose of pembro. Baseline characteristics were generally similar to pt cohorts of historical pembro studies in advanced melanoma. As of the data cutoff date of August 6, 2020, all pts had $\geq$6 mo of follow-up and 40.6% of pts had discontinued study treatment. Median (range) duration of treatment and doses administered were 8.2 mo (1 day–13.9 mo) and 6 (1–11) doses, respectively. Observed exposure with pembro 400 mg Q6W had lower variability than model predictions and was within PK parameters from clinical experience with other pembro regimens (Table). ORR was 50.5% (95% CI 40.4–60.6). 12.9% of pts had CR and 37.6% had PR. Median PFS was 13.8 mo (95% CI 3.0–not reached). Estimated PFS rates were 56.5% at 6 mo and 54.3% at 12 mo. Treatment-related AEs of any grade occurred in 79.2% of pts (grade 3–4: 6.9% of pts; no deaths due to a treatment-related AE). The most common immune-mediated AEs were hyperthyroidism (6.9%) and hypothyroidism (6.9%). **Conclusions:** 1L treatment with pembro 400 mg Q6W yielded a clinically meaningful ORR in pts with advanced melanoma. PK, efficacy and safety results from KEYNOTE-555 Cohort B support prior findings from the model-based assessment and indicate that the benefit-risk profile for the more practical pembro 400 mg Q6W regimen is consistent with that of 200 mg or 2 mg/kg Q3W regimens. Clinical trial information: NCT03665597. Research Sponsor: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

PK metrics; data shown as geometric mean (μg/mL) and 95% CI.

	400 mg Q6W Cohort B[a]	400 mg Q6W model-predicted[b]	200 mg Q3W[c]	2 mg/kg Q3W[c]	10 mg/kg Q2W[c]
Cycle 1					
C_{min}	15.1	10.6	18.1	13.5	119.0
	13.5–16.9	10.4–10.8	17.8–18.3	13.3–13.6	117.1–120.6
C_{max}	127.0	123.0	59.1	44.1	220.3
	121.3–132.7	121.6–124.3	58.5–59.7	43.7–44.5	217.8–222.7
Steady state					
C_{min}	24.0	20.3	30.9	23.1	197.1
	20.6–27.9	19.8–20.9	30.5–31.4	22.7–23.4	193.4–200.2
C_{max}	150.0	147.5	92.8	69.2	428.2
	141.9–158.3	146.1–149.4	91.7–94.1	68.4–70.2	424.0–433.2

[a]Observed data. [b]Simulated using a reference population PK model not including KEYNOTE-555 Cohort B. [c]Simulated using a reference population PK model based on dataset of 2993 pts from KEYNOTE-001, 002, 006, 010, and 024.

Comparing the clinical efficacies of anti-PD-1 antibody monotherapy and anti-PD-1 and anti-CTLA-4 combination therapy as first-line immunotherapy in Japanese advanced acral melanoma: A retrospective, multicenter study (JAMP-neo study).

Yasuhiro Nakamura, Yukiko Kiniwa, Hiroshi Kato, Osamu Yamasaki, Takeo Maekawa, Shigeto Matsushita, Tatsuya Takenouchi, Takashi Inozume, Yasuo Nakai, Satoshi Fukushima, Shintaro Saito, Atsushi Otsuka, Noriki Fujimoto, Taiki Isei, Natsuki Baba, Taisuke Matsuya, Ryo Tanaka, Takahide Kaneko, Masazumi Onishi, Shusuke Yoshikawa; Saitama Medical University International Medical Center, Saitama, Japan; Shinshu University, Matsumoto, Japan; Nagoya-City University, Nagoya, Japan; Okayama University, Okayama, Japan; Jichi Medical University, Tochigi, Japan; National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan; Department of Dermatology, Niigata Cancer Center Hospital, Niigata, Japan; Chiba University, Chiba, Japan; Dermatology, Mie University Hospital, Tsu, Japan; Department of Dermatology and Plastic Surgery, Graduate School of Medical Sciences, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan; Gunma University, Gunma, Japan; Kyoto University, Kyoto, Japan; Shiga University of Medical Science, Shiga, Japan; Department of Dermatology, National Hospital Organization Osaka National Hospital, Osaka, Japan; Fukui University, Fukui, Japan; Asahikawa Medical University, Hokkaido, Japan; Kawasaki Medical School, Kurashiki, Japan; Juntendo University Urayasu Hospital, Urayasu, Japan; Iwate Medical University, Iwate, Japan; Department of Dermatology, Shizuoka Cancer Center, Shizuoka, Japan

Background: Anti-PD-1 antibody monotherapy (PD1) has been commonly used for patients with advanced acral melanoma (AM). However, recent studies have demonstrated the limited clinical efficacy of PD1 in AM compared to non-acral cutaneous melanoma, particularly in nail apparatus melanoma. Although advanced AM patients are strong candidates for first-line anti-PD-1 and anti-CTLA-4 combination therapy (PD1+CTLA4), data on the clinical efficacy of PD1+CTLA4 in AM are lacking. Thus, we aimed to compare the clinical efficacies of PD1+CTLA4 and PD1 in Japanese advanced AM patients. **Methods:** We retrospectively reviewed the clinical records of advanced AM patients treated with PD1+CTLA4 or PD1 as first-line immunotherapy at 23 Japanese institutions. Clinical response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Survival was estimated using Kaplan-Meier analysis. Toxicity was assessed according to CTCAE 4.0. **Results:** A total of 192 patients (median age, 72 years) with advanced AM (palm and sole melanoma, 135; nail apparatus melanoma, 57) were included in the study. PD1+CTLA4 and PD1 were used as first-line immunotherapy in 39 and 153 patients, respectively. The baseline demographics and characteristics were similar between the PD1+CTLA4 and PD1 groups, except for age (median age 67.3 vs. 73.2; $P = 0.005$). The objective response rate (ORR) in PD1+CTLA4 was significantly higher than that of the PD1 group (38.5% vs. 16.3%; $P = 0.047$). The median progression-free survival (PFS) and overall survival (OS) in the PD1+CTLA4 group tended to be longer than those of the PD1 group, but the differences were not significant (median PFS 7.3 months vs. 4.5 months; $P = 0.19$, median OS 43.6 months vs. 18.2 months; $P = 0.19$). In the subgroup analysis of the palm and sole melanoma cohorts, no significant differences in ORR, PFS, and OS were observed between the PD1+CTLA4 and PD1 groups (ORR 31% vs. 20.8%; $P = 0.67$, median PFS 5.3 months vs. 5.9 months; $P = 0.87$, median OS not reached vs. 22.3 months; $P = 0.66$). Meanwhile, the nail apparatus melanoma cohort in the PD1+CTLA4 group exhibited significantly higher ORR, and longer PFS and OS than the PD1 group (ORR 60% vs 6.1%; $P < 0.001$; median PFS 19.6 months vs 3.8 months; $P = 0.008$, median OS 43.6 months vs 13.5 months; $P = 0.049$). Due to immune-related adverse events in all cohorts, the treatment cessation rate was higher in the PD1+CTLA4 group than the PD1 group (59% vs. 11.8%). **Conclusions:** PD1+CTLA4 was clinically more efficacious than PD 1 in advanced AM patients. Notably, advanced nail apparatus melanoma patients were strong candidates for first-line PD1+CTLA4. Research Sponsor: None.

9543 **Poster Session**

Durability of response to immune checkpoint inhibitors (ICI) in metastatic Merkel cell carcinoma (mMCC) after treatment cessation.

Alison Margaret Weppler, Laetitia Da Meda, Ines Silva, Wen Xu, Giovanni Grignani, Alexander M. Menzies, Matteo S. Carlino, Georgina V. Long, Ina Nordman, Christopher Steer, Megan Lyle, Claudia Trojaniello, Paolo Antonio Ascierto, Celeste Lebbe, Shahneen Kaur Sandhu; Peter MacCallum Cancer Centre, Melbourne, Australia; Saint Louis Hospital, APHP, Paris, France; Melanoma Institute Australia, The University of Sydney, Sydney, Australia; Princess Alexandra Hospital, Brisbane, QLD, Australia; Division of Medical Oncology, Candiolo Cancer Institute - FPO, IRCCS, Candiolo (TO), Italy; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Westmead Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Calvary Mater Newcastle Hospital, Waratah, Australia; Border Medical Oncology, Wodonga, Australia; Liz Plummer Cancer Centre, Cairns and Hinterland Hospital and Health Service, Cairns, QLD, Australia; Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori-IRCCS Fondazione "G. Pascale", Naples, Italy; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; APHP Dermatology and CIC, U976, Université de Paris, Hôpital Saint-Louis, Paris, France; Peter MacCallum Cancer Center, Melbourne, VIC, Australia

Background: mMCC is a rare, aggressive neuroendocrine cancer which often occurs in older patients (pts) with multiple comorbidities. While initial response rates to ICI are high, optimal treatment duration, durability of response after treatment cessation and response to retreatment with ICI is unknown. **Methods:** mMCC pts from 12 international centres who received at least one dose of ICI and subsequently stopped treatment without progression for a minimum of 12 weeks were studied. Demographics, disease characteristics and treatment course were examined. **Results:** 40 pts with mMCC were included. Pt characteristics are summarised in Table. Median time on treatment was 13.5 months (range 1 to 35). Median time to best response was 4.5 months (range 1 to 17) and median time receiving treatment after best response was 8 months (range 0 to 29). 25 pts (63%) stopped primarily due to being in a complete or partial response (CR or PR), 9 (23%) due to toxicity and 6 (15%) due to other reasons, primarily pt choice or comorbidities. At time of discontinuation, 30 pts (75%) were in a CR, 8 (20%) in a PR and 2 pts (5%) had stable disease (SD). After a median follow up of 12 months from discontinuation, 14 pts (35%) have progressed (PD); 5 (36%) at a previous site, 5 (36%) at a new site and 4 (29%) at both. PD occurred after a median of 5.5 months (range 4 to 29) off treatment. 4 pts (29%) had a CNS recurrence, none of whom previously had CNS involvement. Pts in CR at time of discontinuation were less likely to progress (CR: 26% PD *vs* non-CR: 67% PD, p=0.044), but still had a considerable rate of PD (CR: 26%, PR: 57%, SD: 100%). Those who progressed had numerically less cycles of ICI prior to treatment cessation (17 *vs* 32, p>0.05). Baseline disease factors, time to best response and duration of treatment after best response were not associated with PD. ICI was restarted in 8 of 14 pts (57%) with PD, with response rate to retreatment of 75% (4 CR, 2 PR, 1 SD, 1 PD – pt with leptomeningeal disease). Median time to best response at retreatment was 3 months (range 2 to 7), with all responses ongoing after a median of 10 months back on treatment. 3 pts had an isolated site of PD successfully treated with radiation therapy and remain in remission off ICI. **Conclusions:** ICI responses in mMCC do not appear as durable off treatment as in other cancers, including in patients who achieve a CR. Ongoing treatment should be considered, though initial data on response to retreatment is promising. Research Sponsor: None.

Patient characteristics.

	N (%)
Age (years)	
Median (range)	75 (52 to 92)
Gender	
Male	29 (73)
Female	11(28)
ECOG Performance Status	
0	13 (33)
1	23 (58)
2	2 (5)
Unknown	2 (5)
Stage	
Unresectable stage III	9 (23)
Stage IV	31 (78)
Number of metastatic sites	
1	21 (53)
2	11 (28)
3	5 (13)
4	3 (8)
Presence of visceral disease	17 (43)
Prior chemotherapy	17 (43)
Baseline immunosuppression	4 (10)
ICI	
Avelumab	36 (90)
Pembrolizumab	3 (8)
Other (Tislelizumab)	1 (3)

Toxicity, response, and survival in older adults with metastatic melanoma treated with checkpoint inhibitors.

Nienke A De Glas, Esther Bastiaannet, Frederiek van den Bos, Simon Mooijaart, Astrid Aplonia Maria Van Der Veldt, Karijn Suijkerbuijk, Maureen J.B. Aarts, Franchette van den Berkmortel, Christian U. Blank, Marye Boers-Sonderen, Alfonsus Johannes Maria van den Eertwegh, Jan Willem de Groot, Geke Hospers, John B. A. G. Haanen, Djura Piersma, Rozemarijn Van Rijn, A. J. Ten Tije, Michel W.J.M. Wouters, Johanna Elisabeth A. Portielje, Ellen Kapiteijn; Leiden University Medical Center, Leiden, Netherlands; Leiden University Medical Centre, Leiden, Netherlands; Departments of Medical Oncology and Radiology & Nuclear Medicine, Erasmus University Medical Center, Rotterdam, Netherlands; UMCU, Utrecht, Netherlands; Maastricht University Medical Center, Maastricht, Netherlands; Zuyderland Hospital, Heerlen, Netherlands; Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Radboudumc, Nijmegen, Netherlands; VU University Medical Center, Amsterdam, Netherlands; Oncological Center Isala, Zwolle, Netherlands; University of Groningen, University Medical Center Groningen, Department of Medical Oncology, Groningen, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; MST, Enschede, Netherlands; Medical Center Leeuwarden, Leeuwarden, Netherlands; Erasmus University Medical Center, Rotterdam, Netherlands; Leiden University Medical Center, Department of Biomedical Data Sciences, Leiden, Netherlands; Haga Hospitals, Den Haag, Netherlands; Leiden University Medical Center, Department of Medical Oncology, Leiden, Netherlands

Background: Checkpoint inhibitors have strongly improved survival of patients with metastatic melanoma. Trials suggest no differences in outcomes between older and younger patients, but only relatively young patients with a good performance status were included in these trials. The aim of this study was to describe treatment patterns and outcomes of older adults with metastatic melanoma, and to identify predictors of outcome. **Methods:** We included all patients aged ≥65 years with metastatic melanoma between 2013 and 2020 from the Dutch Melanoma Treatment registry (DMTR), in which detailed information on patients, treatments and outcomes is available. We assessed predictors of grade ≥3 toxicity and 6-months response using logistic regression models, and melanoma-specific and overall survival using Cox regression models. Additionally, we described reasons for hospital admissions and treatment discontinuation. **Results:** A total of 2216 patients were included. Grade ≥3 toxicity did not increase with age, comorbidity or WHO performance status, in patients treated with monotherapy (anti-PD1 or ipilimumab) or combination treatment. However, patients aged ≥75 were admitted more frequently and discontinued treatment due to toxicity more often. Six months-response rates were similar to previous randomized trials (40.3% and 43.6% in patients aged 65-75 and ≥75 respectively for anti-PD1 treatment) and were not affected by age or comorbidity. Melanoma-specific survival was not affected by age or comorbidity, but age, comorbidity and WHO performance status were associated with overall survival in multivariate analyses. **Conclusions:** Toxicity, response and melanoma-specific survival were not associated with age or comorbidity status. Treatment with immunotherapy should therefore not be omitted solely based on age or comorbidity. However, the impact of grade I-II toxicity in older patients deserves further study as older patients discontinue treatment more frequently and receive less treatment cycles. Research Sponsor: Dutch Research Council (NWO).

	anti-PD(L)1				Ipilimumab				Ipilimumab + nivolumab				
	% of treated patients with toxicity	OR	95% C.I.	p-value	% of treated patients with toxicity	OR	95% C.I.	p-value	% of treated patients with toxicity	OR	95% C.I.	p-value	
Age													
65-74	13.9	Ref		*0.255*	31.9	Ref		*0.859*	41.0	Ref			*0.543*
75+	16.6	1.23	(0.86-1.77)		31.0	0.96	(0.60-1.52)		47.4	1.02	(0.96-1.09)		
Number of comorbidities													
0	12.1	Ref		*0.781*	28.6	Ref		*0.922*	43.9	Ref			*0.410*
1-2	15.3	1.32	(0.71-		32.7	1.22	(0.67-		46.7	1.12	(0.53-		
3 or more	16.0	1.39	2.45)		32.8	1.22	2.20)		34.4	0.67	2.35)		
Unknown	15.8	1.37	(0.75-2.60) (0.35-5.29)		0.0	.	(0.65-2.28)		55.	1.60	(0.30-1.51) (0.37-6.83)		
WHO classification													
0	15.2	Ref		*0.480*	34.3	Ref		*0.321*	47.8	Ref			*0.704*
1	15.1	0.99	(0.66-		25.9	0.67	(0.40-		40.5	0.75	(0.40-		
2	22.4	1.61	1.48)		50.0	1.91	1.12)		45.0	0.89	1.40)		
3 or 4	0.0	.	(0.89-		0.0	.	(0.65-		.	.	(0.34-		
Unknown	11.8	0.75	2.93) (0.34-		27.8	0.74	5.68) (0.34-		28.6	0.44	2.37) (0.13-		
			1.63)				1.61)				1.50)		

9545 **Poster Session**

Results from the phase Ib of the SENSITIZE trial combining domatinostat with pembrolizumab in advanced melanoma patients refractory to prior checkpoint inhibitor therapy.

Jessica Cecile Hassel, Carola Berking, Max Schlaak, Thomas Eigentler, Ralf Gutzmer, Paolo Antonio Ascierto, Bastian Schilling, Svetlana Hamm, Frank Hermann, Philip Gero Reimann, Dirk Schadendorf; Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; University of Erlangen-Nuremberg, Erlangen, Germany; Charité-Universitätsmedizin Berlin, Department of Dermatology, Venereology and Allergology, Skin Cancer Center, Berlin, Germany; Senior Physician, Dermatology Clinic Center for Dermatology Oncology, Universitätsklinikum Und Medizinische Fakultät Tübingen, Tübingen, Germany; Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; University Hospital Würtzburg, Munich, Germany; 4SC AG, Planegg-Martinsried, Germany; Department of Dermatology, University of Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany

Background: Anti-PD-1 +/- anti-CTLA4 antibodies are the current standard of care immunotherapy for advanced melanoma. However, a significant proportion of patients do not achieve disease control. Epigenetic modulation, particularly histone deacetylase (HDAC) inhibition, can overcome tumor escape mechanisms and thus might increase the susceptibility to immunotherapy. **Methods:** Advanced unresectable/metastatic cutaneous melanoma patients primary refractory or non-responding to prior checkpoint inhibitor (CI) therapy were treated with domatinostat at 5 different dose levels (DL) (100 mg (QD), 200 (QD), and 200 mg (BID) using two different schedules (D1-14 and D1-21 q3w) in combination with pembrolizumab (2 mg/kg) q3w to evaluate safety and tolerability. Tumor assessments were performed every 12 weeks and assessed using irRECIST. Sequential tumor biopsies were taken for gene expression analysis and peripheral blood for pharmacokinetic (PK) analysis. **Results:** We report on preliminary results from the phase Ib part of the ongoing study, data cut-off Feb 1st, 2021 a total of 40 patients have been enrolled. Patient characteristics show that the median number of pretreatments at stage IV was 3, 65 % of patients stage M1c (AJCC 7 or 8) and 35 % with elevated LDH at trial inclusion. Treatment emergent adverse events (AEs) related to domatinostat reported in $\geq$ 10% of patients were: diarrhea (23%), nausea (20%), fatigue (20%), rash (15%), pyrexia (13%), blood alkaline phosphatase increased (13%), vomiting (10%), dyspnea (10%), all grade 1 and 2 - except one maculo-papular rash grade 3. In total, 8 patients (20 %) developed $\geq$ grade 3 AEs, with no treatment-related deaths. Patterns of AEs resembled the known safety profiles of domatinostat and pembrolizumab with no increase of immune related AEs for the combination. Maximum tolerated dose was not reached. Four patients discontinued treatment per protocol due to AEs grade 3. We observed clinical activity with 1 complete response, 2 confirmed partial responses and 9 stable diseases (6 confirmed), resulting in a disease control rate of 30% in highly pretreated patients throughout all DLs. Notably, 3 out of 7 patients achieved disease control in DL 3 (domatinostat 200 mg BID D1-14, q3w) and were on treatment $\geq$ 1.5 years, indicating a trend of dose-dependent clinical activity. Domatinostat treatment resulted in a trend to higher intra-tumoral expression of MHC/APM genes and a more inflamed tumor microenvironment reflecting enhanced T cell infiltration. **Conclusions:** The combination of domatinostat and pembrolizumab was safe and well tolerated. The observed clinical activity in advanced melanoma patients refractory to previous checkpoint inhibition and the favorable translational findings warrant further development of domatinostat in combination with CI in melanoma and beyond. Clinical trial information: NCT03278665. Research Sponsor: 4SC AG.

KEYNOTE-629: Health-related quality of life (HRQoL) with pembrolizumab (pembro) in patients (pts) with locally advanced (LA) or recurrent or metastatic (R/M) cutaneous squamous cell carcinoma (cSCC).

Åse Bratland, Eva Muñoz-Couselo, Laurent Mortier, Osama Roshdy, Rene Gonzalez, Jacob Schachter, Ana Maria Arance, Florent Grange, Nicolas Meyer, Abhishek Jagdish Joshi, Salem Billan, Brett Gordon Maxwell Hughes, Jean-Jacques Grob, Karthik Ramakrishnan, Eric (Pingye) Zhang, Burak Gumuscu, Ramona F. Swaby, Ralf Gutzmer; Oslo University Hospital, Oslo, Norway; Vall d'Hebron Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Universite Lille, Centre Hospitalier Regional Universitaire de Lille, Lille, France; McGill University, Montreal, QC, Canada; Centro Estatal de Cancerologiade Chihuahua, Chihuahua, Mexico; Sheba Medical Center at Tel-Hashomer, Ramat Gan, Israel; Hospital Clínic de Barcelona, Barcelona, Spain; CHU Reims–Hôpital Robert Debre, Reims, France; Institut Universitaire du Cancer de Toulouse and Centre Hospitalier Universitaire (CHU), Toulouse, France; Townsville Cancer Centre, Townsville, QLD, Australia; Rambam Health Care Campus, Technion-Israel Institute of Technology, Haifa, Israel; Royal Brisbane and Women's Hospital, Herston, and University of Queensland, Brisbane, QLD, Australia; Aix-Marseille University, Marseille, France; Merck & Co., Inc., Kenilworth, NJ; Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany

Background: KEYNOTE-629 is a single-arm phase 2 study of pembro for cSCC. At second interim analysis (IA), pembro had robust and durable antitumor activity and manageable safety in LA and R/M cohorts. At first IA, pembro maintained HRQoL in the R/M cohort; LA was not analyzed because of ongoing accrual. HRQoL of pts with LA or R/M cSCC at second IA (database cutoff July 29, 2020; additional 15-mo follow-up since IA1 for the R/M cohort) is shown. **Methods:** Pts with LA or R/M cSCC received pembro 200 mg IV Q3W for ≤35 cycles. HRQoL was a prespecified exploratory end point assessed using EORTC QLQ-30 and EuroQol EQ-5D-5L instruments administered at baseline, wk 3, and wk 6; then Q6W through y 1; then Q9W until treatment end/discontinuation; and at the 30-day safety follow-up. HRQoL was analyzed in pts who received ≥1 pembro dose and completed baseline and ≥1 postbaseline HRQoL assessments. Mean change from baseline in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL), physical functioning (PF), and EQ-5D-5L visual analog scale (VAS) scores were evaluated at wk 12 to ensure adequate completion rate and through last pt visit at wk 75 for EORTC QLQ-C30 GHS/QoL and PF scores. HRQoL was categorized as improved or deteriorated based on ≥10-point change in EORTC QLQ-C30 scores (considered clinically meaningful). **Results:** The HRQoL analysis population for LA had 47 pts for EORTC QLQ-C30 and EQ-5D-5L; the R/M cohort had 99 pts for EORTC QLQ-C30 and 100 for EQ-5D-5L. At wk 12, compliance rates were >75% for LA and >80% for R/M cohorts for EORTC QLQ-C30 and EQ-5D-5L. Mean change from baseline to wk 12 was minimal for EORTC QLQ-C30 GHS/QoL, PF, and EQ-5D-5L VAS scores for both cohorts (Table). Mean change from baseline in EORTC QLQ-C30 GHS/QoL and PF scores remained stable over 48 wk in the LA cohort (75-wk data unavailable) and over 75 wk in the R/M cohort. Most pts had improved or stable EORTC QLQ-C30 GHS/QoL and PF scores relative to baseline during follow-up. **Conclusions:** HRQoL was generally maintained with pembro in LA and R/M cSCC cohorts and was not negatively impacted by tumor progression or AEs. Clinical trial information: NCT03284424. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

		Change from baseline to wk 12, mean (95% CI)		Improved + stable,[a,b] % (95% CI)	Deteriorated,[a,c] % (95% CI)
LA cohort	**n**		**n**		
EORTC QLQ-C30 GHS/QoL	31	–0.27 (–10.93, 10.39)	47	76.6 (62.0, 87.7)	23.4 (12.3, 38.0)
EORTC QLQ-C30 PF	31	–1.29 (–8.77, 6.19)	47	74.5 (59.7, 86.1)	25.5 (13.9, 40.3)
EQ-5D-5L VAS	32	2.06 (–7.70, 11.82)	NA	—	—
R/M cohort	n		n		
EORTC QLQ-C30 GHS/QoL	69	4.95 (–1.00, 10.90)	99	71.7 (61.8, 80.3)	28.3 (19.7, 38.2)
EORTC QLQ-C30 PF	69	–3.38 (-8.80, 2.04)	99	64.6 (54.4, 74.0)	35.4 (26.0, 45.6)
EQ-5D-5L VAS	70	1.97 (–3.85, 7.79)	NA	—	—

[a]Change frombaseline to database cutoff. [b]≥10-point increase (improved) or <10-point change (stable) with confirmation at next visit. [c]≥10-point decrease (deteriorated).

9547 **Poster Session**

Checkpoint inhibition in immunosuppressed or immunocompromised patients with advanced cutaneous squamous cell carcinoma (CSCC): Data from prospective CemiplimAb-rwlc Survivorship and Epidemiology (C.A.S.E.) study.

Guilherme Rabinowits, Soo J Park, David M. Ellison, Francis P. Worden, Rhonda W. Gentry, John Strasswimmer, Suraj S. Venna, Michael Robert Migden, Sunandana Chandra, Emily S. Ruiz, Nikita Mehta, Haixin Raymond Zhang, Jennifer McGinniss, Jigar Desai; Department of Hematology/Oncology, Miami Cancer Institute/Baptist Health South Florida, Miami, FL; Division of Hematology and Oncology, University of California San Diego, San Diego, CA; Charleston Oncology, Charleston, SC; Michigan Medicine Rogel Cancer Center, Ann Arbor, MI; CARTI Cancer Center, Little Rock, AR; College of Medicine (Dermatology) and College of Sciences (Biochemistry), Florida Atlantic University, Boca Raton, FL; Inova Schar Cancer Institute Melanoma Center, Fairfax, VA; Departments of Dermatology and Head and Neck Surgery, University of Texas, MD Anderson Cancer Center, Houston, TX; Division of Hematology Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL; Brigham and Women's Hospital, Boston, MA; Sanofi, Cambridge, MA; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Immunosuppressed and/or immunocompromised patients are at increased risk for solid tumors and cutaneous malignancies. Limited data exist on the safety and effectiveness of immune checkpoint inhibitors (ICIs) in these patients because they are frequently excluded from clinical trials. Here, we describe the safety and effectiveness results from the initial cohort of immunosuppressed and/or immunocompromised patients with advanced CSCC enrolled in the C.A.S.E. study (NCT03836105). **Methods:** C.A.S.E. is a prospective, real-world, multi-center, longitudinal study evaluating the effectiveness, safety, quality of life, and survivorship in patients with advanced CSCC treated with cemiplimab. Patients received cemiplimab 350 mg intravenously every 3 weeks per routine standard of care. Patient demographics, disease characteristics, immunosuppression, and relevant medical history were collected. Immunosuppressive regimens varied amongst patients. Investigator assessment of objective response rate (ORR), safety, and tolerability was conducted. Data from 26 immunosuppressed and/or immunocompromised patients with advanced CSCC treated with cemiplimab are presented. Recruitment is ongoing. **Results:** As of November 17, 2020, 121 patients were enrolled in the C.A.S.E. study, of which 26 patients (median age: 74 years [IQR: 71-84]; 85% male; 89% Caucasian) were designated as immunocompromised or immunosuppressed due to a history of solid organ transplant (n = 6), autoimmune disorder (n = 11), or hematologic malignancy (n = 9). Median duration of cemiplimab exposure was 14 months (IQR: 9.1–42, range: 0, 67). Among 19 immunocompromised or immunosuppressed patients who enrolled in C.A.S.E. prior to their third dose of cemiplimab, ORR per investigator assessment was 47% (95% CI: 24–71); 1 (5%) patient had complete response; 8 (42%) had partial response. One patient had a treatment-related serious adverse reaction of organ transplant rejection. One (3.8%) patient discontinued treatment due to increased alanine aminotransferase (not treatment-related). Immune-related AEs (irAEs) occurred in 23% of patients. No treatment-related AEs led to death. **Conclusions:** The safety, tolerability, and effectiveness of cemiplimab in this initial cohort of immunosuppressed and/or immunocompromised patients with advanced CSCC appear to be consistent with those observed in clinical trials that excluded these patients. Further follow-up and additional data would add to our general understanding of safety and effectiveness of anti-PD1 therapy in immunocompromised and/or immunosuppressed patient populations overall. Clinical trial information: NCT03836105. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

9548 **Poster Session**

The influence of harvest method on dendritic cell function and clinical outcomes in a randomized trial of a dendritic cell vaccine to prevent recurrences in high-risk melanoma.

Alexandra Adams, G. Travis Clifton, Timothy J. Vreeland, Anne E. O'Shea, Patrick M. McCarthy, Robert Connor Chick, Phillip M. Kemp Bohan, Annelies Hickerson, Diane F. Hale, John Robert Hyngstrom, Adam C. Berger, James W. Jakub, Jeffrey J. Sussman, Montaser F. Shaheen, Thomas Wagner, Mark B Faries, George Earl Peoples; Brooke Army Medical Center, Fort Sam Houston, TX; Brooke Army Medical Center, San Antonio, TX; The Univ of Utah, Salt Lake City, UT; Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; Mayo Clinic, Rochester, MN; University of Cincinnati, Cincinnati, OH; University of Arizona Cancer Center, Tucson, AZ; Perseus PCI, Greenville, SC; John Wayne Cancer Institute, Santa Monica, CA; Cancer In, San Antonio, TX

Background: A randomized, double-blind, placebo-controlled phase IIb trial of the tumor lysate, particle loaded, dendritic cell (TLPLDC) vaccine was conducted to prevent recurrence in patients (pts) with resected stage III/IV melanoma. Two methods for dendritic cell (DC) harvest were used for vaccine production, including no pretreatment or pretreatment with granulocyte-colony stimulating factor (G-CSF) in an attempt to reduce blood draw volumes. This analysis investigates differences in clinical outcomes and RNA gene expression between these DC harvest methods for TLPLDC vaccine creation. **Methods:** The TLPLDC vaccine is created by loading autologous tumor lysate into yeast cell wall particles (YCWPs) and exposing them to phagocytosis by DCs. By investigator/pt choice, pts had 120mL of blood drawn for DC harvest, or pts received 300μg of G-CSF for pre-DC mobilization and a 50-70 mL blood draw 24-48 hours later. Total vaccine production time was 72 hrs. Pts were randomized 2:1 to receive TLPLDC or placebo (DCs exposed to empty YCWPs). 1-1.5 x10^6 cells/dose were injected intradermally at 0, 1, 2, 6, 12, and 18 months. Differences in disease free survival (DFS) and overall survival (OS) were evaluated by Kaplan Meier analysis between pts who did not receive pretreatment (TLPLDC), pts who did receive pretreatment with G-CSF (TLPLDC+G), and pts receiving placebo. RNA-seq analysis was performed on the total RNA of pts' prepared TLPLDC vaccines to assess gene expression. Relative RNA expression (RRE) was compared between TLPLDC and TLPLDC+G. **Results:** As previously reported, 144 pts were randomized: 103 received TLPLDC (46 TLPLDC, 57 TLPLDC+G) and 41 received placebo. There were no significant clinicopathologic or treatment differences between the three treatment arms. Survival was significantly improved in TLPLDC compared to TLPLDC+G or placebo, including 36-month OS (92.9% vs 62.8% vs 72.3% respectively, p = 0.022) and DFS (51.8% vs 23.4% vs 27.1%, p = 0.027). When compared to TLPLDC+G (n = 3) vaccine, RNA-seq from TLPLDC vaccine (n = 3) showed upregulation of genes associated with DC maturation, including HLA-DMB (RRE: 3.60), IFIT1 (3.38), CD27 (3.26), IFI44L (3.24), MX1 (2.96), HLA-DQA1 (2.67), HLA-DRA (2.40), CD49D (2.34) and CD74 (2.09), while downregulated genes were associated with DC suppression or immaturity including SERPINA1 (RRE:7.8), TLR2 (6.65), CCR1 (5.11), IL10 (4.19), CD93 (3.84) and CD14 (3.25). **Conclusions:** Pts receiving TLPLDC vaccine had significantly improved OS and DFS, while outcomes remained similar between those who received TLPLDC+G vs placebo. Pts who did not receive G-CSF had higher expression of genes linked to DC maturation and antigen processing and presentation, likely explaining the improvement in clinical efficacy. A phase III trial to further assess the TLPLDC vaccine to prevent recurrence is planned. Clinical trial information: NCT02301611. Research Sponsor: Elios Therapeutics.

9549 **Poster Session**

Survival outcomes associated with fewer combination ipilimumab/nivolumab doses in advanced-stage melanoma.

Vincent T Ma, Yilun Sun, Merna Sitto, Jessica Waninger, Leslie Anne Fecher, Michael Green, Christopher D. Lao; University of Michigan, Ann Arbor, MI; Department of Radiation Oncology, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI; Michigan Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, MI

Background: Standard combination ipilimumab/nivolumab (I/N) is given as 4 induction doses for advanced stage melanoma. While many patients receive less than 4 doses due to treatment-related toxicities, it is unclear if fewer doses of I/N may still provide long term clinical benefit. Our aim is to determine if response assessment after 1 or 2 doses of I/N can predict long-term survival and if fewer doses of I/N can achieve similar survival outcomes. **Methods:** We performed a single-center, retrospective analysis on a cohort of patients with metastatic or unresectable melanoma from 2012 to 2020 who were treated with standard I/N. Cox regression of progression free survival (PFS) and overall survival (OS) models were performed to assess the relationship between response assessment after 1 or 2 doses of I/N and risk of progression and/or death. Clinical benefit response (CBR) was assessed, defined as SD (stable disease) + PR (partial response) + CR (complete response) by imaging or physical examination. Among patients who achieved a CBR after 1 or 2 doses of I/N, a multivariable Cox regression of survival was used to compare 3 or 4 vs 1 or 2 doses of I/N adjusted by age, gender, pre-treatment LDH level, BRAF mutation status, primary melanoma site, time to initial assessment, brain metastasis, and liver metastasis. **Results:** 199 patients were identified and considered evaluable in our study. Median follow up was 28.8 months. Patients with CBR after 1 dose of I/N had improved PFS (HR: 0.23, 95% CI 0.14-0.39; p<0.001) and OS (HR: 0.19, 95% CI 0.10-0.38; p<0.001) compared to progressive disease (PD) [Table]. Patients with CBR (vs PD) after 2 doses of I/N also had improved PFS (HR: 0.17, 95% CI 0.11-0.26; p<0.001) and OS (HR: 0.13, 95% CI 0.07-0.23; p<0.001) [Table]. The survival risk comparing 3 or 4 vs 1 or 2 doses of I/N were HR 0.82 (95% CI 0.45-1.53; p=0.540) for PFS and HR 0.56 (95% CI 0.24-1.30; p=0.175) for OS. **Conclusions:** Clinical benefit response (CBR) after 1 or 2 doses of I/N may be predictive of long-term survival in advanced stage melanoma. Patients who have CBR after 1 or 2 doses of I/N may achieve a similar survival benefit with fewer doses of I/N. Longer follow up and prospective studies are warranted to validate our findings. Research Sponsor: None.

			Progression-Free Survival		Overall Survival	
Response assessment		n	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
After 1 dose of I/N	PD	46	1.00		1.00	
	CBR (SD+PR+CR)	82	0.23 (0.14 - 0.39)	<0.001	0.19 (0.10 - 0.38)	<0.001
After 2 doses of I/N	PD	49	1.00		1.00	
	CBR (SD+PR+CR)	122	0.17 (0.11 - 0.26)	<0.001	0.13 (0.07 - 0.23)	<0.001

9550 **Poster Session**

Complete responders to checkpoint inhibitors in advanced melanoma: Relapse risk factors, and patients' outcomes.

Amelie Dutheil, Djaouida Belkadi, Marine Antigny, Severine Roy, Jeremy Lupu, Anaïs Vallet, Emilie Routier, Caroline Robert; Dermatology Unit, Gustave Roussy Cancer Institute, Villejuif, France; Biostatistical Analysis, Gustave Roussy Cancer Institute, Villejuif, France; Clinical research, Gustave Roussy Cancer Institute, Villejuif, France; Dermatology Department, Gustave Roussy Cancer Institute, Villejuif, France; Dermatology Unit, Gustave Roussy Cancer Institute, Villejuif Cedex, France; Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France

Background: Since the development of immune checkpoint inhibitors (ICI) for advanced melanoma, a small group of patients with an excellent and durable response has emerged. Complete response (CR) is achievable in about 10-20% of the patients and seem to have an excellent prognosis. However, 10 to 15% of them might relapse eventually. Our main objective was to determine factors associated with relapse after a CR to ICI in advanced melanoma. The second objective was to describe relapse modalities and tumor response to subsequent treatments. **Methods:** We performed a single-center, retrospective study, in 141 patients with a CR to ICI for advanced melanoma, treated at Gustave Roussy (France) from January 2010 to June 2020. CR was confirmed on two consecutive CT-scanner or PET-CT at least 3 months apart. Characteristics of the patients at diagnosis, during and after treatment were compared in both groups: CR with relapse and CR without relapse. The LASSO analysis, a statistical analysis using lambda penalization coefficient for prognostic studies, was performed regarding the many statistical variables analysed. **Results:** At data analysis, immunotherapy was interrupted in 94.3% of the patients and the median follow-up was 3.5 years since immunotherapy discontinuation. Eventually, 18 of 141 patients (12.8%) had relapsed and 126 (87.2%) had not. The statistical analysis identified three factors associated with melanoma recurrence: prior lines of therapy, the type of melanoma and the mutation status. Indeed, relapse risk was higher in patients with wild type melanoma (as opposed to BRAF or NRAS mutant melanoma), with a mucosal, acral or unknown primitive melanoma and who received prior lines of treatment. Other factors such as demographical characteristics, tumor burden, metastasis localization, type or grade of toxicity, pseudo progression, type of ICI, treatment duration, use of a complementary local treatment and pursuit/discontinuation of immunotherapy were not statistically associated with the duration of the complete response. In case of melanoma recurrence, reintroduction of immunotherapy provided tumor response in half of our patients: 13 of the 18 relapsing patients received immunotherapy after melanoma recurrence; allowing 3 CR, 2 partial responses and 1 stable disease. One third of the relapsing patients eventually died of disease progression. **Conclusions:** This study confirmed the excellent prognosis of CR to ICI in advanced melanoma, even after treatment discontinuation and identified 3 baseline factors associated with a risk of relapse: absence of BRAF or NRAS mutation, primary of acral, mucosal or unknown origin, and previous lines of therapy. Rechallenge with ICI was effective in 50% of the patients. Research Sponsor: None.

9551 **Poster Session**

The risk and tropism of central nervous system metastases (CNS) in patients with stage II cutaneous melanoma.

Paul Johannet, Min Jae Kim, Melissa Call, Nicholas Gulati, Judy Zhong, Janice M. Mehnert, Iman Osman; NYU Grossman School of Medicine, New York, NY; New York University Grossman School of Medicine, New York, NY

Background: Recent data suggest that patients with stage III melanoma are at high enough risk for developing CNS metastases to consider routine surveillance neuroimaging (Journal of Clinical Oncology; PMID: 31990608). Given that a subset of stage II patients have a worse prognosis than stage III patients, we investigated the risk of developing brain metastases in stage II disease and compared it to the risk in stage III disease. **Methods:** We studied a cohort of prospectively enrolled melanoma patients who had protocol driven follow-up at New York University (NYU) Langone Health. We investigated both the incidence and time to development of CNS metastases, and explored whether the frequency of CNS metastases as a first isolated site of distant disease varies among the different stages. **Results:** The study cohort included a total of 1,102 patients (stage II: n = 619 with median follow-up 56.5 months; stage III: n = 483 with median follow-up 40.9 months). 85/619 (14%) stage II and 91/483 (19%) stage III patients developed CNS metastases (p = 0.03). The estimated 5-year cumulative incidence was 9% in stage IIA, 14% in stage IIB, and 29% in stage IIC patients (p = 0.0001). It was 10% in stage IIIA, 32% in stage IIIB, 23% in stage IIIC, and 49% in stage IIID (p = 0.0001). The CNS was the site of first metastasis for 32/154 (21%) stage II patients who developed distant disease compared to 28/214 (13%) stage III patients (p = 0.06). **Conclusions:** A subset of stage II patients are at an elevated risk for developing CNS metastases within 5 years of their initial diagnosis, which is comparable to that seen in stage III patients. The frequency of the CNS as a first site of metastasis in stage II melanoma suggests a propensity for brain tropism that cannot only be explained by a generalized pro-metastatic phenotype. Surveillance strategies that incorporate serial neuroimaging should be considered for these individuals. Research Sponsor: U.S. National Institutes of Health.

9552 **Poster Session**

Impact of systemic therapy sequencing on overall survival for patients with advanced BRAF-mutated melanoma.

B. Adi Kartolo, Jasna Deluce, Wilma M. Hopman, Linda Liu, Tara D. Baetz, D. Scott Ernst, John Gordon Lenehan; Division of Medical Oncology, Queen's University, Kingston, ON, Canada; London Regional Cancer Program, London, ON, Canada; Department of Public Health Sciences-Queen's University, Kingston, ON, Canada; Pulse Infoframe, London, ON, Canada; Division of Medical Oncology, Department of Oncology, London Regional Cancer Program, London Health Sciences Centre and University of Western Ontario, London, ON, Canada

Background: Both immune checkpoint inhibitors (ICI) and BRAF targeted therapy (TT) are effective treatments for patients with advanced BRAF-mutated melanoma. However, the choice of first-line (1L) therapy is at the discretion of treating oncologists without clear guidance from current available data or established guidelines. Utilizing prospectively collected data from the Canadian Melanoma Research Network (CMRN) database, we provide real-world evidence to highlight the impact of sequencing these therapies. **Methods:** Prospective data from 9 cancer centres in Canada was retrieved from the CMRN database for patients with unresectable/metastatic melanoma, with BRAF targetable subtypes, who received at least one-cycle of 1L palliative-intent ICI or TT, and at least 1-year of follow-up. We categorized patients into 2 groups: 1L BRAF±MEK inhibitors with/without subsequent PD-1±CTLA-4 inhibitors (1L-TT), or vice versa (1L-ICI). The primary study outcome was overall survival (OS). Survival outcomes were analyzed through Kaplan-Meier methods, and multivariable Cox analysis was utilized to account for potential confounders. **Results:** Our study (N=235) included 152 and 83 patients in 1L-TT and 1L-ICI groups, respectively. Combined BRAF-MEK inhibitors accounted for 59% of the 1L-TT group, whereas single-agent IO accounted for 66% of the 1L-ICI group. There were 93 patients who received second-line (2L) therapy, with a non-significant trend of 1L-TT group receiving more 2L therapy compared to 1L-ICI group (65% vs. 43%, P=0.404). Neither treatment group showed significant differences in median time on 1L therapy (P=0.645) or 2L therapy (P=0.686). The 1L-ICI group was associated with a favourable median overall survival (OS) compared to 1L-TT group (19.3 vs. 10.0 months, P=0.031). Specifically, the ICI only group had the highest median OS, followed by TT-ICI sequence, ICI-TT sequence, and TT only groups respectively (not reached vs. 38.3 vs. 16.9 vs. 6.1 months, P<0.001). However, this OS benefit (HR 0.89, 95% 0.51-1.53, P=0.644) was non-significant upon controlling for confounders such as baseline metastatic sites >2 (HR 2.07, 95%CI 1.24-3.46, P=0.006) and ECOG ≥2 (HR 3.47, 95%CI 2.02-5.97, P<0.001) in multivariable Cox analysis. **Conclusions:** There was no significant difference in OS between 1L-TT and 1L-IO groups. Rather, OS is driven mostly by the patient's clinical status and tumour-associated features. Our study provides real-world evidence in an understudied area. Further studies are needed to validate our findings to inform guideline development. Research Sponsor: None.

Multivariable Cox analysis of study population (N=99).

	Overall Survival		
	HR	**95% CI**	**P-Value**
Number of Metastatic Sites >2	2.07	1.24-3.46	0.006
Presence of Brain Metastasis	1.66	0.951-2.90	0.074
ECOG ≥2	3.47	2.02-5.97	<0.001
Sequencing Group 1L-TT (Reference)	0.89	0.51-1.53	0.664

9553 **Poster Session**

IL-6 blockade for prophylaxis and management of immune-related adverse events (irAEs) with anti-PD-1 based immunotherapy.

Florentia Dimitriou, Sabrina A Hogan, Phil F Cheng, Reinhard Dummer, Alexander M. Menzies, Georgina V. Long; Melanoma Institute Australia, Sydney, Australia; University Hospital Zurich, Zurich, Switzerland; Skin Cancer Center, University Hospital of Zürich, Zürich, Switzerland; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia

Background: Immune checkpoint inhibitors (ICIs) have activity across many tumor types, but activation of the immune system may also lead to significant, often steroid-refractory irAEs. We sought to determine the activity of tocilizumab, an anti-IL6R monoclonal antibody (mAb), in treatment or prevention of auto-immune irAE in ICI-treated patients (pts). **Methods:** Institutional databases from 2 melanoma centers were reviewed for pts treated with ICIs and tocilizumab. Treatment and melanoma outcomes were prospectively assessed. Longitudinal assessment of c-reactive protein (CRP) and assessment of clinical improvement (defined as irAE resolution to grade $\leq$1 CTCAEv5) or prophylaxis (absence of flare, defined as $\geq$ grade 2) were utilized to evaluate the benefit of tocilizumab. Paired Wilcoxon rank test was used to compare CRP levels prior to ICI administration, at the onset of irAEs and after tocilizumab administration. **Results:** 22 pts were identified. 2 pts were treated prophylactically (pre-existing dermatomyositis [n = 1] and giant cell arteritis [GCA, n = 1]) before the administration of PD1. 20 pts were treated for management of irAEs due to PD1 +/-CTLA4 (multiple concurrent irAEs [n = 3], steroid refractory irAES [hepatitis & pancreatitis, n = 2], steroid+anti-TNFα refractory colitis [n = 2], steroid+-other immunosuppressive-refractory hepatitis [n = 1], cytokine release syndrome-related AEs [n = 6], musculoskeletal irAEs [n = 6]). 15 (68.2%) pts with irAEs required hospitalization and of those, 13 (86.7%) received tocilizumab whilst inpatient. Median time to irAE onset from ICI start was 48 days (range 8-786) and from irAE onset to tocilizumab administration 32 days (range 1-192). Median time to irAE resolution from tocilizumab administration was 7 days (range 1-799). Clinical improvement/benefit was demonstrated in 21/22 patients; one patient with ir-hepatitis did not respond. Median CRP prior to ICI administration was 32mg/L (range 0.3-99), at the onset of irAE 49.5mg/L (range 0.3-251, p = 0.055) and after the tocilizumab administration 18mg/L (range 0.3-18, p = 0.0015). Tocilizumab was well tolerated with self-limiting and transient toxicities in 17 (77.3%) patients. There were two grade 4 events; gastrointestinal tract perforation and Fournier gangrene, the latter unrelated to tocilizumab. Two (9%) patients died due to melanoma. From start of ICI, median progression-free survival (PFS) was 5.88 months and median overall survival (OS) was not reached. **Conclusions:** Tocilizumab was a well-tolerated and effective steroid-sparing treatment for both management of irAEs, as well as prevention of a flare of pre-existing auto-immune disorders during ICI administration. Prospective trials to evaluate its efficacy and impact on cancer outcomes compared with standard strategies are required.
Research Sponsor: None.

9554 **Poster Session**

Safety and efficacy of HX008: A humanized immunoglobulin G4 monoclonal antibody in patients with locally advanced or metastatic melanoma—A single-arm, multicenter, phase II study.

Bin Lian, Yu Chen, Di Wu, Zhiguo Luo, Zhengyun Zou, Yu Jiang, Hongming Pan, Qingxia Fan, Jianfu Zhao, Qing Xu, Renbing Jiang, Chuanliang Cui, Xuan Wang, Fang Lou, Zhen Guo, Lu Si, Zhihong Chi, Xinan Sheng, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Fujian Provincial Cancer Hospital, Fuzhou, China; The First Hospital of Jilin University, Changchun, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Nanjing Drum Tower Hospital, Nanjing, China; West China Hospital of Sichuan University, Chengdu, China; Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China; Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China; The First Affiliated Hospital of Jinan University, Guangzhou, China; Department of Oncology, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China; Affiliated Cancer Hospital of Xinjiang Medical University, Urumchi, China; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; The First Hospital Of Jilin University, Changchun, China

Background: HX008 is a new recombinant humanized anti-PD-1 monoclonal antibody, belonging to human IgG4 / kappa subtype, which can selectively block the binding of PD-1 with its ligands PD-L1 and PD-L2. **Methods:** In this single arm phase 2 trial, eligible patients (pts) were aged from18 to 75, who previously failed with conventional treatment for locally advanced or metastatic melanoma, with an ECOG performance status of 0 or 1 and had measurable lesions according to the RECIST criteria (V1.1). Ocular melanoma, brain metastasis or previous use of anti PD-1 ab were excluded. Pts received HX008 3mg/kg every 3 weeks, until disease progression, intolerable toxicity or treatment discontinuation for any other reasons. The primary endpoint was ORR according to RECIST criteria, and the secondary endpoints were OS, PFS, DCR and the toxicity. The iRECIST criteria would also be used in the evaluation of response and treatment discontinuation. Clinical trial information: NCT04749485. **Results:** From Oct 2018 to Jan 2021, 119 pts have been eligible and enrolled. Basic characteristics: median age 59 years; 57 males (42.9%) ; stage 22%, stage 78%; primary: acral 52.1%, mucosal 19.3%, cutaneous 18.5% and unknown 10.1%; Gene mutation status: Braf 10.9%, Nras 9.2%, cKit 4.2%; condition of previous treatments: 67.26%, 25.21%,7.56% pts had received 1st, 2nd and 3rd line or above treatments respectively (chemotherapy 69.7%, targeted therapy 15.1%, immunotherapy 43.7%). The ORR according to RECIST V1.1 and iRECIST was 18.49% (1CR, 21 PR, 95% CI 11.96-26.64) and 20.17% (1 iCR, 23 iPR,95% CI 13.37-28.50), respectively. For PD-L1 positive pts the ORR was 15.09% (95%CI 6.75-27.60) and 12% for negative (95%CI 10.98-32.83). For different subtypes, the ORR was 36.36% for cutaneous melanoma, 14.52% for acral primary, 8.7% for mucosal primary, and 25% for unknown primary. The DCR and iDCR was 44.54% and 47.06%, respectively. With a median follow up time of 13.2 months, the median PFS was 3.25 months (95% CI 2.0, 4.1) and the PFS rate at 1 year was 25.8% (95%CI 17.19,35.33). The median OS was 17.91 months (95% CI 13.08,NR) and the OS rates at 1 year was 63.9% (95% CI 53.02, 73.00). Median DOR has not reached and the DOR and iDOR rates at 1 year were 80.64% and 87.39%, respectively. TRAEs occurred in 89.9% of the pts, with grade 3/4 AEs 31.9%, the followings were those incidences $\geq$1%, hyperglycemia (2.5%), elevated aspartate aminotransferase (1.7%), elevated serum bilirubin (1.7%), elevated serum creatine phosphokinase (1.7%), elevated lipase (1.7%), hypoalbuminemia (1.7%), hypokalemia (1.7%) and diabetic ketoacidosis (1.7%). **Conclusions:** HX008 shows its efficacy and safety in locally advanced or metastatic melanoma pts in the treatments of 2nd line or above. Randomized controlled studies are now on pending. Clinical trial information: NCT04749485. Research Sponsor: Taizhou Hanzhong biomedical co. LTD.

9555 **Poster Session**

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

Erika Richtig, Ralf Gutzmer, Carmen Loquai, Jochen Utikal, Christoph Hoeller, Rudolf Stadler, Andrea Forschner, Jessica Cecile Hassel, Daniela Goeppner, Michael Fluck, Sebastian Haferkamp, Martin Kaatz, Manfred Welslau, Reinhard Dummer, Roger Anton Fredy Von Moos, Andrea Schmidt, Laura Milde, Olivier Michielin, Dirk Schadendorf; Department of Dermatology, University of Graz, Graz, Austria; Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany; Department of Dermatology, University Medical Center Mainz, Mainz, Germany; Skin Cancer Unit, DKFZ and Medical Faculty Mannheim of Heidelberg University, Mannheim, Germany; Department of Dermatology, Medical University of Vienna, Vienna, Austria; Department of Dermatology, Medical Center Minden, Minden, Germany; Department of Dermatology, University Hospital of Tuebingen, Tuebingen, Germany; Department of Dermatology, Heidelberg University Hospital, NCT Heidelberg, Heidelberg, Germany; Department of Dermatology, Justus-Liebig-University, Giessen, Germany; Department of Internal Medicine, Fachklinik Hornheide, Muenster, Germany; Department of Dermatology, University Hospital of Regensburg, Regensburg, Germany; SRH Wald-Klinikum Gera, Gera, Germany; Oncological Practice Aschaffenburg, Aschaffenburg, Germany; Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland; Department of Medical Oncology, Kantonsspital Graubuenden, Chur, Switzerland; Alcedis GmbH, Giessen, Germany; Pierre Fabre Pharma GmbH, Freiburg, Germany; Center of Personalized Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland; Department of Dermatology, University Hospital Essen, Essen, Germany

Background: For the treatment of advanced $BRAF^{V600}$-mutated melanoma, targeted therapy (BRAF/MEK-inhibition) is a standard of care. Encorafenib + binimetinib (EB) were approved in the EU in Sep 2018 and in Switzerland in Nov 2019, based on positive results from COLUMBUS (NCT01909453), with a median progression-free survival (PFS) of 14.9 mo (4-year PFS: 26%) and overall survival (OS) of 33.6 mo (4-year OS: 39%). As data from controlled trials are based on selected populations, $BERING^{MELANOMA}$ investigates the use of EB under real-world conditions in a broader population. **Methods:** $BERING^{MELANOMA}$ is an ongoing, multi-national, multi-center, prospective, longitudinal, non-interventional study. It analyzes the effectiveness, quality of life and tolerability of EB-treatment under real-world conditions (primary endpoint: 1-year PFS-rate), focusing on the first- (1L) and second-line setting and including an evaluation of the impact of prognostic factors. The project aims to enroll up to 750 patients (pts) in a total of 80 German, Austrian and Swiss sites with a study duration of 8 yrs. So far, from Oct 2019 to Jan 2021, 153 pts have been included. Pts with prior BRAF-/MEK-inhibition (except adjuvant use completed $>$ 6 mo) and $>$ 1 prior treatment line were excluded. **Results:** Here we present the first planned interim analysis based on the initial 100 enrolled pts (91 treated / 89 evaluable; median follow-up: 8.1 mo). This analysis set shows a median age of 63.0 yrs (range 29.0-88.0), 52% of pts were female. 81% presented with distant metastases (brain: 31%), with an involvement of $\geq$3 organ systems in 51% and an elevated LDH in 42%. 54% of pts underwent prior systemic therapy (adjuvant: 28%; 1L: 24%, with ipilimumab + nivolumab as main 1L-treatment: 52%). EB was mainly administered in the 1L-setting (65%). Main reasons for EB-selection were: physician's preference (37%), efficacy (34%), quality of life (21%). Median estimated EB treatment duration was 12.7 mo (95%CI 8.3-NE), median relative dose intensity was 100% for both drugs. Treatment adaptations were required in 34% of pts. Adverse events (AE) were reported in 76% of pts (grade 3/4: 26%). Main AE ($\geq$10%, all grades) were: nausea (18%), diarrhea (17%), CK increase (15%), fatigue (11%), gamma-GT increase (11%). No fatal toxicities were observed. **Conclusions:** This first interim analysis of $BERING^{MELANOMA}$ shows an investigation of EB in a real-world population with advanced disease. Despite the poorer prognosis configuration as compared to the pivotal study, the observed treatment duration and tolerability profile are largely consistent with data derived from COLUMBUS without any new safety signals. The second interim analysis will be performed after enrollment of 200 pts and will include an initial analysis of effectiveness data. Clinical trial information: NCT04045691. Research Sponsor: Pierre Fabre Pharma GmbH (Germany), Pierre Fabre Pharma Austria (Austria), Pierre Fabre Pharma AG (Switzerland).

9556 **Poster Session**

Plasma thymidine kinase activity (TKa) as a novel prognostic biomarker in metastatic melanoma.

Hildur Helgadottir, Fernanda Costa Svedman, Marie Jalsenius, Veronica Hoiom, Samuel Rotstein, Suzanne Egyhazi Brage, Vitali Grozman, Fabian Söderdahl, Lars Ny, Mattias Bergqvist; Department of Oncology-Pathology, Stockholm, Sweden; Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; Karolinska University Hospital, Stockholm, Sweden; Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden; Karolinska Institute, Stockholm, Sweden; Karolinska University Hospital, Sweden, Sweden; Statisticon, Stockholm, Sweden; Sahlgrenska University Hospital, Gothenburg, Sweden; Biovica International, Uppsala, Sweden

Background: In the recent decade, new effective immunotherapies and targeted therapies have emerged for the treatment of disseminated melanoma. However, a considerable fraction of patients does not respond or get lasting effects and the treatments also have significant side effects. Biomarkers can contribute with more knowledge on prognosis and the efficacy of these therapies in different patients. In other cancer types, the plasma activity of the enzyme thymidine kinase (TKa), has been demonstrated as a marker of tumor stage and prognosis. The TK enzyme is part of a reaction chain to introduce thymidine into the DNA strand. TK thereby has a key function in DNA-synthesis, -repair and cell division. Dividing cells release TK during mitotic exit and TK can thus be detected in the blood. This study is the first to investigate plasma TKa as a potential biomarker in melanoma patients. **Methods:** Plasma samples were collected within five days prior to treatment start in patients with unresectable metastatic cutaneous melanoma, treated with immunotherapy (anti-CTLA-4 and/or anti-PD-1) or targeted therapy (BRAF±MEK inhibitors). Plasma TKa levels were determined using the DiviTum TKa ELISA assay (Biovica, Sweden). TKa levels were correlated with the patients' baseline criteria, response rate (RR), progression free survival (PFS) and overall survival (OS). **Results:** Among the 124 study patients, the median TKa was 50 Du/L (range $<$ 20-3491 Du/L). Significantly higher plasma TKa levels were found in patients with ECOG performance status $\geq$1 vs. 0-1 ($P<$ 0.001), M1c-d vs. M1a-b disease ($P<$ 0.001), $\geq$3 vs. 1-2 affected organs ($P=$ 0.002) or elevated vs. non-elevated LDH ($P<$ 0.001). In the patients treated with immunotherapy (n = 86) the RR was 63.2% vs. 37.9% in those with low ($<$ 60 Du/L) vs. high TKa ($P=$ 0.024). The median PFS and OS was 19.9 and $>$ 60 months in those with low TKa vs. 12.6 and 18.5 months in those with high TKa (HR for PFS: 1.73 (95% CI, 1.01-2.97), $P=$ 0.044 and HR for OS: 2.16 (95% CI, 1.17-3.98), $P=$ 0.011). In the patients treated with BRAF±MEK inhibitor (n = 38) a similar trend was observed, with shorter PFS and OS in those with high TKa, but the differences were not statistically significant. **Conclusions:** In this first study on plasma TKa in melanoma patients, high pretreatment TKa was significantly associated with poor baseline factors and poor response and survival in immunotherapy treated patients. Currently, plasma LDH is the only non-clinical factor that is routinely used as a prognostic marker in melanoma. Several other candidate markers have been described, such as PD-L1 tumor immunohistochemistry, tumor mutational burden, gut microbiome and circulating tumor DNA. Compared to these assays, TKa measured with DiviTum is a simpler, ELISA based test for a single plasma marker. TKa is hence a novel and interesting marker in melanoma and should be further studied to define its role as a prognostic and predictive marker in this disease. Research Sponsor: Swedish Cancer Society.

9557 **Poster Session**

Outcomes of non-treatment naive melanoma patients with central nervous system relapse.

Thiago Pimentel Muniz, Hadee Lone, Diana Paola Arteaga, Diana Gray, Maysa Tamara Silveira Vilbert Pereira, Luke Mantle, Raviya Singh, Sofia Genta, Samuel Saibil, David Hogg, Anna Spreafico, Marcus O. Butler; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; School of Medicine, University of Toronto, Toronto, ON, Canada; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Melanoma has a high probability of central nervous system (CNS) spread. Although first line nivolumab and ipilimumab resulted in 56% response rate and 29.2 months median overall survival (OS) in patients with melanoma brain metastases (MBM), there is paucity of data for patients who develop MBM after prior systemic therapy. As this subgroup is often underrepresented in clinical trials, we aimed to evaluate the OS of non-treatment naïve patients who develop MBM and identify factors related to survival. **Methods:** In this single-center, retrospective study, consecutive melanoma patients with $>$ 90 days from exposure to either immune checkpoint inhibitor (ICI), targeted therapy (TT), or chemotherapy, to CNS relapse were included. OS was defined as the time between CNS relapse and death by any cause. The Log-Rank method was used to calculate OS. Cox regression analysis was used to identify differences between subgroups. Variables with a p value < 0.1 were included in a multivariate model. A p value < 0.05 was considered statistically significant. **Results:** Between 2012 and 2018, 135 patients were identified. Median age was 57 (29-92) years, 92 (68%) were male, and median number of prior systemic therapies was 2 (1-6). One-hundred and nine (81%) patients had cutaneous melanoma; acral lentiginous melanoma (ALM) comprised 11 (8%) patients. Molecular studies were available for 123 patients, of whom 61 (50%) were *BRAF* V600 mutant. Eighty-nine (66%) patients had prior ICI, of whom 33 (37%) had prior exposure to both anti-PD1 and anti-CTLA-4, either as monotherapy or combination. Amongst the *BRAF* V600 mutant population, 48 (79%) had prior TT. Radiotherapy was given to 112 patients, of whom 55 (49%) had SRS. Median follow-up was 41 (95% CI 30-51) months. Median OS was 6.4 (95% CI 5.3-7.5) months. Patients with ALM, $>$ 3 MBM, ECOG 2-4 and active treatment at CNS relapse ($<$ 30 days from last dose of treatment to MBM diagnosis) were at increased risk of death, whilst subsequent treatment with ICI was related to better survival (Table). On multivariate analyses, age ($p = 0.007$), subtype ($p = 0.04$), number of MBM ($p = 0.01$), active treatment at CNS relapse ($p < 0.001$) and subsequent ICI ($p = 0.002$) remained statistically significant. Exploratory analyses suggested subsequent treatment with anti-PD1 + anti-CTLA-4 (n = 42) compared favourably to subsequent anti-CTLA-4 only (n = 21) (13 x 7 months, $p = 0.004$), and was independent of prior ICI. **Conclusions:** Previously treated melanoma patients who develop MBM have a poor prognosis, but subsequent ICI therapy seems to be associated with better OS. Further clinical investigation to identify optimal anti-PD1-based therapies is warranted for non-treatment naïve patients who develop MBM. Research Sponsor: None.

Variable	HR (IC 95%)	*p* value
ALM subtype (vs. other cutaneous)	2.3 (1.02-5.1)	0.04
> 3 MBM	1.7 (1.07-2.8)	0.02
ECOG 2-4	2.7 (1.4-5.0)	0.001
Active Treatment	2.3 (1.4-4.0)	0.001
Subsequent ICI	0.3 (0.2-0.5)	< 0.001

BRAF and *NRAS* mutation status and response to checkpoint inhibition in advanced melanoma.

Olivier Jules van Not, Alfonsus Johannes Maria van den Eertwegh, John B. A. G. Haanen, Christian U. Blank, Maureen J.B. Aarts, Franchette van den Berkmortel, Jan Willem de Groot, Geke Hospers, Ellen Kapiteijn, Djura Piersma, Rozemarijn Van Rijn, Marion Stevense, Astrid Aplonia Maria Van Der Veldt, Gerard Vreugdenhil, Marye Boers-Sonderen, Han J. Bonenkamp, Anne M.L. Jansen, Willeke Blokx, Michel W.J.M. Wouters, Karijn Suijkerbuijk; University Medical Center Utrecht, Leiden, Netherlands; VU University Medical Center, Amsterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Maastricht University Medical Center, Maastricht, Netherlands; Zuyderland Hospital, Heerlen, Netherlands; Oncological Center Isala, Zwolle, Netherlands; Groningen University Medical Center, Groningen, Netherlands; Leiden University Medical Center, Department of Medical Oncology, Leiden, Netherlands; MST, Enschede, Netherlands; Medical Center Leeuwarden, Leeuwarden, Netherlands; Amphia Hospital, Department of Internal Medicine, Breda, Netherlands; Departments of Medical Oncology and Radiology & Nuclear Medicine, Erasmus University Medical Center, Rotterdam, Netherlands; Radboudumc, Nijmegen, Netherlands; Department of Pathology, University Medical Center Utrecht, Utrecht, Netherlands; UMC Utrecht, Utrecht, Netherlands; Leiden University Medical Center, Department of Biomedical Data Sciences, Leiden, Netherlands; UMCU, Utrecht, Netherlands

Background: The ability to analyze tumor mutation profiles has altered the oncology treatment landscape over the past decades. However, little is known about the effect of specific gene mutations on the response to immune checkpoint inhibitors (ICIs) in patients with advanced melanoma. **Methods:** All unresectable stage IIIc and IV patients with *BRAF* V600, *NRAS* mutations and *BRAF* and *NRAS* wild-type patients treated with anti-PD-1 or ipilimumab-nivolumab between 2012 and 2020 were included from the Dutch Melanoma Treatment Registry, a nationwide population-based registry. Outcomes were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). A Cox model was used to analyze the association of possible prognostic factors with PFS and OS. **Results:** In total 1358 first-line patients treated with anti-PD-1 and 524 treated with ipilimumab-nivolumab were included. Median follow-up was 25.6 months for anti-PD-1 treated patients and 16.3 months for ipilimumab-nivolumab treated patients. The highest ORR, in first-line, to anti-PD-1 was in patients who were *BRAF* and *NRAS* wildtype (50.2%), compared to *BRAF* V600 (43.8%) and *NRAS* mutated patients (49.8%). ORR to ipilimumab-nivolumab was highest in *NRAS* mutated patients (44.9%), while ORR was 39.5% for *BRAF* mutated patients and 40.3% for wild-type patients. Median PFS in the anti-PD-1 treatment regimen was significantly higher ($p = 0.049$) for double wild-type patients (16.7 months) patients than for *BRAF* mutated patients (9.9 months) and *NRAS* mutated patients (11.3 months). PFS was not significantly different ($p = 0.11$) in the ipilimumab-nivolumab treatment cohort, with a median PFS of 6.5 months for the wild-type group, 10.8 months for the *BRAF* group, and 9.1 months for the *NRAS* group. In the anti-PD-1 treated patients, median OS was significantly higher ($p < 0.001$) for *BRAF* mutated patients (32.8 months) compared to *NRAS* (21.0 months) and wild-type patients (23.0 months). For ipilimumab-nivolumab treated patients, median OS was also significantly higher ($p < 0.001$) for *BRAF* mutated patients (36.5 months) than for *NRAS* mutated patients (11.8 months) and wild-type patients (16.1 months). After adjustment for potential confounders, the presence of a *BRAF* mutation remained associated with lower PFS in the anti-PD-1 treatment cohort and better OS in both treatment cohorts. Higher age, higher ECOG score, elevated LDH levels, liver metastases and brain metastases were associated with worse survival. **Conclusions:** PFS in first-line PD-1 was significantly higher for double wild-type patients than for *BRAF* mutant and *NRAS* mutant patients. PFS in ipilimumab-nivolumab treated patients did not significantly differ between *BRAF* mutant, *NRAS* mutant and double wild-type patients. OS was significantly higher for *BRAF* mutant patients in both treatment strata, which is probably the result of the subsequent BRAF/MEK-inhibition treatment option in this group. Research Sponsor: None.

9559 **Poster Session**

A phase 1b clinical trial of anti-PD-1 ab (Toripalimab) plus intralesional injection of OrienX010 in stage melanoma with liver metastases.

Jun Guo, Chuanliang Cui, Xuan Wang, Bin Lian, Shanshan Yin, Yue Cong, Zhihong Chi, Lu Si, Xinan Sheng, Bixia Tang, Lili Mao, Xue Bai, Xieqiao Yan, Siming Li, Li Zhou; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Department of Ultrasound, Peking University Cancer Hospital & Institute, Beijing, China; Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: Liver metastasis was associated with reduced responses and PFS in melanoma patients (pts) treated with anti-PD-1 monotherapy, which is probably due to reduced marginal CD8+ T cell infiltration. Oncolytic virotherapy was found to increase CD8+ T cell infiltration in the injected lesions and improve the efficacy of anti-PD-1 ab in a phase 1b trial. We hypothesized that intratumoral oncolytic virus injection for liver metastasis in melanoma combined with systemic anti-PD-1 therapy might improve the efficacy, thus conducting this phase 1b trial with intratumoral OrienX010 - a HSV-1-derived oncolytic virotherapy with expression of GM-CSF combined toripalimab in liver metastatic melanoma pts. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extra-hepatic metastasis; ocular melanoma and brain metastasis were excluded. Pts received intravenous toripalimab Q2W combined with ultrasound guided intratumoral injection of OrienX010 Q2W (8×10^7 pfu/ml, 10ml per injection) until intolerance or disease progression per iRECIST criteria. Liver biopsy would be performed at baseline and first tumor evaluation (8-12weeks). The primary endpoint was toxicity; secondary endpoints included ORR, DCR and PFS. Clinical trial information: NCT04206358. **Results:** From Jul 2019 to Dec 2020, 15 pts were eligible and enrolled. Baseline characteristics: median age 62 yrs; primary: mucosal 60%, cutaneous 20%, unknown primary 13.3%, acral 6.7%; gene mutation status: Braf 20%, Nras 6.7%; 73.3% got extra-hepatic metastasis: regional or distant lymph node 46.7%, lung 20.0%; LDH > ULN 20%; median size of injected lesions: 32mm(10-83mm); median number of liver metastasis: 4(1-10); median number of injection: 10 (3-36). AEs were all grade 1/2: pyrexia 86.7%, rigor 66.7%, elevated transaminase 53.3%, nausea/vomiting 40.0%, fatigue 26.7%. No grade 3-4 AEs. The ORR by investigator was 13.3% (2/15), DCR 46.7% (7/15); the response rate was 40%(6/15) for injected lesions, 28.5%(4/14) for non-injected lesions in liver, and 23% (3/13) for extra-hepatic metastasis. For biopsies of injected lesions at 8 to 12weeks, 30%(2 PR and 3 SD) showed no melanoma cells residual by immunohistochemistry, 46.7% got impressive TIL infiltration (Brisk n = 4 and Nonbrisk n = 3 according to the definition of AJCC 8th edition) compared with baseline in which all showed absence of TIL infiltration, also a large number of plasma cells, histiocyte and pigment were found with hyaline fibrosis. The PFS has reached 72 weeks for one PR pt. The median PFS was not reached. **Conclusions:** Systemic toripalimab combined with intrahepatic OrienX010 injection has shown remarkable pathological responses with good tolerance in melanoma liver metastases. Survival is still in follow-up. Clinical trial information: NCT04206358. Research Sponsor: Oriengene Biotechnology Ltd.

9560 **Poster Session**

Pyrexia-related outcomes upon application of an adapted pyrexia management algorithm in patients (pts) with *BRAF* V600: Mutant unresectable or metastatic melanoma treated with dabrafenib plus trametinib (DabTram) in the COMBI-i trial.

Paolo Antonio Ascierto, Caroline Robert, Paul D. Nathan, Reinhard Dummer, Hussein Abdul-Hassan Tawbi, Keith T. Flaherty, Antoni Ribas, Dirk Schadendorf, Steven Green, Lali Sandalic, Mike R. Lau, Tonatiuh Romero, Georgina V. Long; Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori-IRCCS Fondazione "G. Pascale", Naples, Italy; Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; Mount Vernon Cancer Centre, Northwood, United Kingdom; University Hospital Zürich Skin Cancer Center, Zürich, Switzerland; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital, Boston, MA; University of California, Los Angeles, CA; Comprehensive Cancer Center (Westdeutsches Tumorzentrum), University Hospital Essen, German Cancer Consortium (DKTK)-Heidelberg, Essen, Germany; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Background: First-line DabTram has shown long-term efficacy in pts with *BRAF* V600–mutant unresectable or metastatic melanoma in the Phase III COMBI-d and COMBI-v trials. Data from the Phase III COMBI-i trial comparing spartalizumab plus DabTram vs placebo plus DabTram (pbo-DabTram) demonstrated efficacy in the pbo-DabTram arm, consistent with historical data. Pyrexia (single preferred term [PT]) is the most common adverse event (AE) reported with DabTram (pooled COMBI-d [data cutoff: Jan 12, 2015] and COMBI-v [data cutoff: Apr 17, 2014]: any grade, 54.2%; grade ≥ 3, 5.4%; serious pyrexia AEs leading to hospitalization, 11.8%). A new pyrexia management algorithm was implemented in the COMBI-i trial to improve pyrexia-related outcomes. We report pyrexia-related outcomes in pts treated with pbo-DabTram in the control arm of COMBI-i part 3. **Methods:** COMBI-i (NCT02967692) part 3 is a double-blind, Phase III trial in which pts with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma were randomized 1:1 to receive spartalizumab (400 mg intravenously every 4 weeks) plus Dab (150 mg orally twice daily) and Tram (2 mg orally once daily) vs pbo-DabTram. In the adapted pyrexia management algorithm, both Dab and Tram are interrupted promptly at the first symptom of pyrexia or its associated prodrome (ie, chills, rigors, night sweats, or influenza-like symptoms). Treatment at the same dose level is restarted upon the improvement of symptoms if pts are symptom free for ≥ 24 hours. Pyrexia incidence rates presented are for the single PT of pyrexia. **Results:** At data cutoff (July 1, 2020), median follow-up was 27.2 mo for all pts enrolled in COMBI-i part 3 (N = 532). In the DabTram control arm, 52.7% (139/264) and 3.0% (8/264) of pts had any-grade and grade ≥ 3 pyrexia, respectively. Serious pyrexia AEs were reported in 6.1% (16/264), which led to hospitalization in 5.3% (14/264). Pyrexia led to dose interruption of both Dab and Tram in 39.0% (103/264), with 1.5% (4/264) permanently discontinuing both agents. Median relative dose intensity was 97.8% for Dab and 97.7% for Tram. **Conclusions:** Pyrexia-related outcomes, including grade ≥ 3 pyrexia (3.0% vs 5.4%) and serious pyrexia AEs leading to hospitalization (5.3% vs 11.8%), were improved in pts treated with DabTram in COMBI-i part 3 compared with historical data from COMBI-d/v. The adapted algorithm offers a simplified approach for managing pyrexia, thereby reducing the incidence of severe pyrexia while maintaining consistent efficacy with DabTram. Clinical trial information: NCT02967692. Research Sponsor: Novartis.

9561 **Poster Session**

Treatment outcomes in patients (pts) with melanoma brain metastases (MBM) treated with systemic therapy: A systematic literature review (SLR) and meta-analysis.

Hussein Abdul-Hassan Tawbi, Georgina V. Long, Nicolas Meyer, Boris Breznen, Charmy Vyas, Lisa Leung, Andriy Moshyk, Divya Pushkarna, Pratik K. Thakkar, Mir Sohail Fazeli, SRIVIDYA KOTAPATI, Dirk Schadendorf; The University of Texas MD Anderson Cancer Center, Houston, TX; Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; Institut Universitaire du Cancer de Toulouse and Centre Hospitalier Universitaire (CHU), Toulouse, France; Evidinno Outcomes Research Inc., Vancouver, BC, Canada; Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Uxbridge, United Kingdom; Department of Dermatology, University of Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany

Background: The introduction of immunotherapy and targeted therapy has revolutionized the treatment landscape for metastatic melanoma. However, clinical trial data in pts with MBM are scarce; here we summarize the available clinical evidence. **Methods:** An SLR was conducted by searching EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials databases through November 13, 2020. When available, KaplanMeier (KM) curves for overall survival (OS) were digitized and converted to pseudo-individual pt data using the Guyot algorithm. A meta-analysis of the pooled KM curves was performed for selected interventions, including immunotherapies and targeted therapies. Median OS was calculated either through the meta-analysis of KM curves or as a weighted average of median OS (table). When interventions were reported in only 1 study, the value reported was used instead of the weighted average and compared qualitatively with the other results. Results for treatment modalities other than systemic agents will also be presented. **Results:** The SLR included 70 publications that evaluated systemic therapies in pts with MBM for qualitative evidence synthesis: 12 pertaining to 7 randomized controlled trials, 55 pertaining to 46 single-arm studies, and 3 involving nonrandomized comparative studies. The pt population was highly heterogeneous with respect to prior therapies, pt characteristics, and neurological symptoms. For the meta-analysis, a total of 25 KM curves from 12 studies representing 6 interventions and 1043 pts were digitized. Based on the pooled KM curves, median OS was numerically longer with nivolumab plus ipilimumab (NIVO + IPI; 28.3 mo; 95% CI, 19.731.9) than with the other interventions (range 5.711.8 mo; table). Similar OS benefit was also observed with NIVO + IPI when the weighted average of the median was used (in a long-term study, median OS was 29.2 mo) compared with the other interventions. **Conclusions:** Given the lack of comparative clinical trial data in pts with MBM, there remains an unmet need to determine the best approach to treat these pts. This analysis suggested a clinical advantage with NIVO + IPI compared with other systemic agents analyzed. The heterogeneity of the available data added uncertainty to our treatment assessments. Therefore, these findings warrant further research into the best approach to improve outcomes in pts with MBM. Research Sponsor: Bristol Myers Squibb.

	Pooled KM curves				Weighted samples			
Treatment	No. of studies	No. of KM curves	Pooled sample size, n	Median OS, mo (95% CI)	No. of studies	No. of cohorts	Pooled sample size, n	Median OS, mo
IPI	3	5	230	5.7 (4.66.8)	2	4	199	6.3
NIVO	1	3	41	9.8 (5.516.0)	1	2	41	13.3
NIVO + IPI	3	4	156	28.3 (19.731.9)	1	1	27	29.2[a]
Dabrafenib (DAB)	1	4	172	7.3 (not available)	1	4	172	6.9
Vemurafenib	4	5	319	11.8 (9.415.0)	4	6	382	12.5
DAB + trametinib	1	4	125	8.3 (6.99.7)	1	4	125	8.7
Pembrolizumab					1	1	23	17[a]

[a]As reported.

9562 **Poster Session**

Efficacy of cetuximab after immunotherapy (IO) in advanced cutaneous squamous cell carcinoma (CSCC).

Julian Andres Marin-Acevedo, Bethany Withycombe, Youngchul Kim, Zeynep Eroglu, Joseph Markowitz, Andrew S. Brohl, Ahmad A. Tarhini, Kenneth Yee Tsai, Nikhil I. Khushalani; Moffitt Cancer center, Tampa, FL; H Lee Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Canter and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; H. Lee. Moffitt Cancer Center & Research Institute, Tampa, FL; Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center, Tampa, FL

Background: Anti-PD1 (aPD1) monotherapy with cemiplimab-rwlc or pembrolizumab is now considered standard of care for first-line management of advanced CSCC not amenable to surgery or curative radiotherapy. Previously chemotherapy or anti-EGFR agents were commonly used for these patients albeit with modest efficacy and limited duration of response. In prospective evaluation, the overall response rate (ORR) to cetuximab was 28% with disease control rate (DCR) of 69% at 6 weeks. The efficacy of second-line treatment following primary or acquired resistance to aPD1 therapy is not known. We investigated the activity of cetuximab in patients who progressed on previous IO therapy. **Methods:** We performed a single institution retrospective review from 9/28/18 (US approval date of cemiplimab-rwlc for CSCC) through 11/30/20 of patients with locally advanced or metastatic CSCC who received cetuximab after prior IO therapy. We identified patients who received cetuximab either immediately following IO therapy (cohort A) or as a subsequent line not immediately following IO therapy (cohort B). Primary endpoint was ORR with secondary endpoints of DCR, survival and toxicity. Median follow-up and survival times were calculated using the Kaplan-Meier method. **Results:** Thirteen patients, median age 72 years (62-82), all Caucasian, and 11 males (85%) were included in this study. Eleven pts received cetuximab immediately post-IO progression; two had additional intervening therapy post-IO before receiving cetuximab. Three patients received concurrent radiotherapy (palliative or definitive) with cetuximab. The ORR to cetuximab was 54% (7/13) including 1 complete and 6 partial responses. The cumulative 6-month DCR was 77%. All responses were observed in cohort A; both patients in cohort B had progressive disease as best response. Six of 7 initial responses are ongoing, including 3 in whom cetuximab was discontinued. At a median follow-up of 9.1 months, the median PFS has not been reached for the entire cohort. There were no unanticipated toxicities to cetuximab with rash (77%) and hypomagnesemia (54%) being the most common adverse events. **Conclusions:** In advanced CSCC, cetuximab used immediately after progression on aPD1 therapy yields notably higher and durable overall response than previously reported in the pre-IO therapy era. If validated in a larger dataset, this should be the preferred therapy for second-line treatment in advanced CSCC. Further exploration into the mechanism of this high efficacy of anti-EGFR therapy post aPD1 therapy is warranted. Research Sponsor: None.

9563 **Poster Session**

External validation of a Dutch predictive nomogram for complete response to T-VEC in an independent American patient cohort.

Emma H.A. Stahlie, Michael Carr, Jonathan S. Zager, Alexander Christopher Jonathan Van Akkooi; Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

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. Recently, Stahlie et al. published (Cancer Immunol Immunother '21) a model for predicting a complete response (CR) to T-VEC based on 3 easily accessible tumor characteristics identified using univariable and multivariable logistic regression analysis. The aim of this study was to externally validate this model in an independent, American patient cohort. **Methods:** A total of 76 patients with stage IIIB-IVM1a melanoma treated with T-VEC at Moffitt Cancer Center were included. A second nomogram was built incorporating the same predictive factors: tumor size (diameter of largest metastasis in mm), type of metastases (cutaneous, subcutaneous and nodal) and number of metastases (cut-off: <20 and >20). Predictive accuracy was assessed through calculation of overall performance, discriminative ability, and calibration. Outcomes and previously published outcomes were compared. Statistical analyses were done using R software. **Results:** Overall performance of the validation dataset nomogram was calculated with the Brier score and found to be 0.195, demonstrating good overall performance and similar to the original model Brier score of 0.182. Discriminative power, assessed by calculating the area under the receiver operating characteristic (ROC) curve was similar for both models, 0.767 and 0.755 for the NKI and Moffitt, respectively, resulting in a fair discriminative ability. The calibration curve showed mostly slight underestimation for predicated probabilities >0.37 and slight overestimation <0.37. **Conclusions:** An independent dataset externally validated a recently published predictive nomogram for CR to T-VEC in stage IIIB-IVM1a melanoma, with both models resulting in overall performances that were comparable and good. The second model reinforces the conclusion that for the best response to T-VEC, it should be used early on in the course of the disease, when the patient's tumor burden is cutaneous with smaller diameter and fewer of metastases. Research Sponsor: None.

Clinicopathologic characteristics of both cohorts.

	Dutch (n=93)	American (n=76)
Median age (years, range)	69 (30–97)	77 (47 – 94)
Gender		
Male	40	42
Female	53	34
Location		
Head/neck	12	18
Upper extremity	2	13
Trunk	15	5
Lower extremity	64	40
Median Breslow depth (mm, range)	2.7 (0.5 – 8.2)	2.4 (0.4 – 15)
Ulceration		
Yes	28	24
No	48	43
Unknown	17	9
Stage at T-VEC		
3B	30	29
3C	56	40
3D	6	1
4 (M1a)	1	6
Median number of lesions (range)	7 (1 – 130)	4 (1 – 40)
Median diameter largest lesion (mm, range)	20 (0.5-100)	10 (4 – 86)
Metastasis subtype		
Cutaneous (dermal only)	32	25
Subcutaneous(subdermal +/- dermal)	53	46
Lymph nodes(nodal +/- subdermal +/- dermal)	8	5
Overall response rate	79%	71%
Complete response rate	62%	51%

9564 **Poster Session**

Outcomes of BRAF mutant metastatic melanoma (MM) patients (pts) after cessation of targeted therapy (TT) with BRAF or BRAF/MEK inhibitor(i).

Natalie Jackson, Theresa Rodgers, Ida John, Denai R. Milton, Lauren Elaine Haydu, Rodabe Navroze Amaria, Adi Diab, Jennifer Leigh McQuade, Sapna Pradyuman Patel, Hussein Abdul-Hassan Tawbi, Michael K.K. Wong, Michael A. Davies, Isabella Claudia Glitza; The University of Texas MD Anderson Cancer Center, Houston, TX; UT MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX

Background: Since their introduction into the clinic a decade ago, BRAF and BRAF/MEKi have dramatically changed the outcomes of pts with BRAF mutant MM. While typically, these agents are administered until progression (PD), other reasons for stopping TT include unacceptable toxicity, complete response to treatment, or pt/physician decision or preference. The outcomes for MM pts that stop TT for reasons other than PD are largely unknown. Here we report the clinical features and outcomes of the largest cohort of MM pts who stopped TT for reasons other than PD to date. **Methods:** Under an institutionally approved database, we identified MM pts treated at the MD Anderson Cancer Center with BRAF±MEK inhibitors, and their records were reviewed to identify pts that stopped TT for reasons other than PD. Pts demographics, treatment information and clinical outcomes were recorded. Overall survival (OS) time was computed from three start dates (initial diagnosis, initial unresectable stage III melanoma, 1st dose of TT) to last known vital sign. Pts alive at the last follow-up date were censored. Time to recurrence was computed from date of 1st dose of TT to recurrence. Pts who did not experience disease recurrence were censored The Kaplan-Meier method was used to estimate OS and time to recurrence. **Results:** A total of 58 pts were identified, 32 (55%) were male. Most pts had a BRAF V600E (n = 49) or V600K (n = 6) mutation. At TT initiation median age was 59.5 years (range 29- 95), LDH was within normal range in 46 (85%), median number of prior systemic therapies was 1 (range 0-5), with 50% of pts receiving prior systemic therapy. Most (n = 33; 57%) pts were treated with single agent BRAFi (12 with dabrafenib, 11 vemurafenib). Among pts treated with combination TT (n = 25), most received dabrafenib with trametinib (n = 21; 84%). Median TT treatment duration was 9.5 months (range 0.03-80.5 months). Reasons for TT discontinuation were unacceptable toxicity (n = 29; 50%) and pt or physician decision/preference in responding patients (n = 23; 40%). At time of TT discontinuation, 48% of pts had achieved a complete response (CR), 28% a partial response (PR), and 22% stable disease (SD), 1 patient had unknown disease status. With standard follow-up, after stopping TT, 40 pts (69%) have recurred or experienced PD, with a median time to recurrence of 14.9 months (95% CI:7.8-26.3 months). At PD, 32 (76%) of pts had new metastatic sites. After PD 26 pts (63%) pts received BRAF/MEKi, 11 (44%) achieved a CR and 6 (24%) a PR, and 5 (20%) for a response rate of 88%; while 3 (12%) pt had PD as best response and 1 was unknown. For the full cohort, the median OS from time of 1st dose of TT was 6.4 years. **Conclusions:** Among MM pts who stopped TT for reasons other than PD, the majority of pts recurred, but most responded to re-introduction of TT. This information can help to inform discussion with pts regarding cessation of, or re-challenge with, TT. Research Sponsor: Cancer Center Support Grant.

9565 **Poster Session**

Multicentre retrospective assessment of toxicity and response to immunotherapy in elderly patients with metastatic melanoma.

Shivanshan Pathmanathan, Hari S Babu, Robert Mason, Saw Htut, Zulfiquer Ali Otty, Megan Lyle, Marcin Radoslaw Dzienis; Department of Oncology, Gold Coast University Hospital, Gold Coast, QLD, Australia; Liz Plummer Cancer Centre, Cairns and Hinterland Hospital and Health Service, Cairns, Australia; Department of Oncology, Townsville University Hospital, Townsville, QLD, Australia; Liz Plummer Cancer Centre, Cairns and Hinterland Hospital and Health Service, Cairns, QLD, Australia

Background: The incidence of melanoma increases with age, however, elderly patients remain underrepresented in landmark immunotherapy trials for metastatic melanoma. This study aims to investigate the impact of age on efficacy and toxicity of immunotherapy, and complications of immunosuppression to treat toxicity. **Methods:** A multicentre retrospective study involving centres in Australia [Gold Coast University Hospital, Cairns Base Hospital, Townsville University Hospital] was performed to compare the efficacy and toxicity of immunotherapy in metastatic melanoma in patients ≥70 years versus patients < 70 years treated between 2015 and 2019. Data collected included: baseline demographics, PFS, OS, Grade 3 or higher (Gr3+) adverse events as per CTCAEv5, adverse events leading to discontinuation, duration of steroids used to treat toxicity and complications secondary to steroids. Comparison of survival outcomes between the groups was calculated using Kaplan Meier, Log rank test and multivariate Cox regression analysis. Fisher exact test was used to determine differences in toxicity between the two groups. **Results:** A total of 229 patients were included with 106 patients ≥70years and 123 patients < 70 years. Baseline demographics were similar. Dual immunotherapy (ipilimumab + nivolumab) was less commonly used in patients ≥70years [13 v 38% $p < 0.001$]. Although the median PFS was numerically higher amongst ≥70years [10.8 v 6.9months $p = 0.99$], the landmark PFS was not [3yr PFS: 31 v 39%; 4yr PFS: 22 v 39%]. The median OS was similar in patients ≥70 years v < 70years [27.5 v 28.7 months $p = 0.91$], with similar landmark survival [3yr OS: 46 v 49%; 4yr OS: 42 v 49%]. Age was not associated with a difference in overall survival on multivariate analysis. There was no increase in Gr3+ adverse events in patients ≥70 years [22 v 21% $p = 1.00$] or discontinuation rates [26 v 20% $p = 0.35$]. There was one death in a patient < 70years secondary to colitis. There was a significantly higher rate Gr3+ adverse events in ≥70years patients receiving dual immunotherapy [71 v 35% $p = 0.029$] and a similar rate of Gr3+ adverse events with PDL1 inhibitors [13 v 11% $p = 0.7$]. Median duration of steroids was similar in both group [15 v 17wks], as was the median duration of high dose steroids defined as greater than 10mg of prednisone [5 v 6wks]. Complications of steroids was numerically higher in the elderly population [42 v 25% $p = 0.15$]. The most common adverse event to immunosuppression was infection. **Conclusions:** Patients ≥70years received similar benefit from immunotherapy in comparison to their younger counterparts. Toxicity related to PDL1 inhibitors was similar in both groups and was higher in patients ≥70years receiving dual immunotherapy. Patients ≥70 years had a clinically significant higher rate of complications secondary to steroids. Research Sponsor: None.

Health-related quality of life (HRQoL) in patients (pts) with locally advanced basal cell carcinoma (laBCC) treated with cemiplimab: Analysis of a phase II, open-label clinical trial.

Alexander J. Stratigos, Chieh-I Chen, Cristina Ivanescu, Karl D. Lewis, Ketty Peris, Oliver Edgar Bechter, James Harnett, Vera Mastey, Matthew Reaney, Christina Daskalopoulou, Patrick R. LaFontaine, Gerasimos Konidaris, Denise Bury, Suk Young Yoo, Kosalai Kal Mohan, Ebony Coates, Timothy Geoffrey Bowler, Matthew G. Fury, Aleksandar Sekulic; University of Athens, A. Sygros Hospital, Athens, Greece; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; IQVIA, Durham, NC; University of Colorado Cancer Center, Aurora, CO; Catholic University Fondazione Policlinico Universitario, Rome, Italy; UZ Leuven, Leuven, Belgium; Sanofi, Cambridge, MA; Mayo Clinic, Scottsdale, AZ

Background: Cemiplimab-rwlc is the first immunotherapy to receive approval in the US, fully for pts with laBCC and accelerated for metastatic BCC, post hedgehog inhibitors or for whom hedgehog inhibitors are not appropriate. Cemiplimab resulted in clinically meaningful anti-tumor activity in pts with laBCC who progressed on or were intolerant to hedgehog inhibitor therapy (NCT03132636). This analysis evaluated HRQoL in these pts. **Methods:** Adults with laBCC and ECOG performance status $\leq$1 (n=84) received IV cemiplimab 350 mg Q3W for up to 9 treatment cycles. At baseline (BL) and day 1 of each cycle (C), pts completed EORTC QLQ-C30 and SKINDEX-16 questionnaires that assess Global Health Status (GHS)/QoL, functioning, and BCC-related symptoms. Mixed-effects repeated measures (MMRM) models were used to estimate least squares (LS) mean (standard error [SE]) change from BL during treatment (i.e., across C2 to C9); changes $\geq$|10| points were considered clinically meaningful. Responder analyses were conducted in pts with non-missing data from BL to determine the proportions with clinically meaningful improvement or deterioration, or stability on QLQ-C30 and SKINDEX-16 at C2 and C9; a 10-point threshold was considered meaningful for both instruments. **Results:** BL scores showed moderate to high levels of functioning and low symptom burden. In MMRM models, overall changes from BL on QLQ-C30 indicated stability for GHS/QoL and all scales except for clinically meaningful worsening of fatigue (LS mean [SE] change 12.5 [3.9]; $P<.05$). In responder analysis, the majority of pts reported clinically meaningful improvement or stability at C2 and C9 on all QLQ-C30 functioning scales and the key symptom of pain but not fatigue (Table). On SKINDEX-16, MMRM models showed clinically meaningful improvement on the emotional subscale (LS mean [SE] change –13.2 [3.9]; $P<.05$) and stability on the symptom and functional subscales. Responder analysis showed clinically meaningful improvements or stability across the SKINDEX-16 subscales in approximately 80% of pts at C2, and 70–80% of pts at C9. **Conclusions:** In laBCC pts treated with cemiplimab, the majority reported clinically meaningful improvement or stability in GHS/QoL and functional status while maintaining a low symptom burden except for fatigue. Clinical trial information: NCT03132636. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

Number (%) of pts with clinically meaningful improvement or stability/clinically meaningful deterioration.

	C2	C9
GHS/QoL	63 (87.5)/9 (12.5)	10 (58.8)/7 (41.2)
Physical functioning	58 (77.3)/17 (22.7)	14 (77.8)/4 (22.2)
Role functioning	52 (69.3)/23 (30.7)	11 (61.1)/7 (38.9)
Emotional functioning	60 (81.1)/14 (18.9)	12 (66.7)/6 (33.3)
Cognitive functioning	56 (75.7)/18 (24.3)	13 (72.2)/5 (27.8)
Social functioning	60 (81.1)/14 (18.9)	11 (61.1)/7 (38.9)
Pain	56 (74.7)/19(25.3)	14 (77.8)/4 (22.2)
Fatigue	46 (61.3)/29 (38.7)	8 (44.4)/10 (55.6)

9567 **Poster Session**

Pathology of durable stable disease in melanoma patients treated with ipilimumab, nivolumab, or ipilimumab, and nivolumab combination therapy.

Elizabeth Iannotti Buchbinder, Kathleen L. Pfaff, Michael P. Manos, Olivia Ouyang, Patrick Alexander Ott, Scott J. Rodig, F. Stephen Hodi; Dana-Farber Cancer Institute, Boston, MA; Dana–Farber Cancer Institute, Boston, MA; Department of Pathology and Center for Immuno-Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: As immunotherapy with checkpoint blockade becomes the backbone of melanoma treatment there is a need to better understand the biology associated with long term benefit. One particularly interesting set of patients are those with prolonged stable disease or response with residual findings on imaging. It is unknown if immunotherapy has led to scarring at the site of prior disease or if there are residual tumor cells being controlled by an ongoing immune response. Evaluating tissue from patients with prolonged responses provides a unique opportunity to determine the composition of residual lesions. Correlation with PET/CT helps determine if this is an accurate modality to reflect presence of residual viable tumor tissue. **Methods:** Metastatic melanoma patients that have attained long term stable disease after treatment with ipilimumab, nivolumab, or ipilimumab plus nivolumab were identified. Patients must have received ipilimumab, nivolumab or combination therapy 2+ years prior to enrollment and must have had stable disease for $\geq$ 6 months. Patients were consented and underwent PET/CT scans and biopsies of residual areas of stable disease. Pre- and post-treatment tissue samples underwent pathologic assessment to look at tumor cell content, fibrotic content, and inflammation. **Results:** Ten patients were consented for evaluation but only 7 met the screening criteria and underwent PET/CT and tissue biopsy. Six patients had FDG avid lesions on PET/CT which ranged in intensity from SUV 2.4-22. One patient had no FDG avidity in the areas of residual disease observed on CT. Biopsies from the residual stable lesions demonstrated predominantly necrosis and fibrosis with prominent pigment containing macrophages. One patient with an axillary nodal lesion with an SUV of 22 had active melanoma on pathology which was resected, and the patient has subsequently remained without progression of disease. **Conclusions:** Patients with durable stable disease after treatment with ipilimumab, nivolumab or ipilimumab and nivolumab combination therapy represent a unique population of melanoma patients treated with immune checkpoint inhibition. An examination of the residual lesions observed in these patients demonstrated predominantly necrosis and fibrosis consistent with resolving lesions. The presence of melanophages in these samples may suggest some ongoing immune surveillance. One patient did demonstrate residual melanoma suggesting the need for ongoing monitoring of this patient population. Research Sponsor: Bristol Myers. Squib.

9568 **Poster Session**

Tumor PD-L1 expression and gene panel mutational profile as outcome predictors of PD-1-based checkpoint inhibition therapy in metastatic melanoma: A prospective multicenter DeCOG study.

Selma Ugurel, Klaus Griewank, Susanne Horn, Rudolf Herbst, Patrick Terheyden, Jochen Utikal, Claudia Pföhler, Jens Ulrich, Alexander Kreuter, Peter Mohr, Ralf Gutzmer, Friedegund Elke Meier, Edgar Dippel, Antje Sucker, Jan-Malte Placke, Eva Hadaschik, Jürgen C. Becker, Michael Weichenthal, Dirk Schadendorf, Dermatologic Oncology Group (DeCOG); Department of Dermatology, University Hospital Erlangen and Department of Dermatology, University of Würzburg, Essen, Germany; University Hospital of Essen, Essen, Germany; Department of Dermatology, University of Duisburg-Essen, Essen, Germany; HELIOS Hauttumorzentrum Erfurt, Erfurt, Germany; Department of Dermatology, Allergy, and Venereology, University of Lübeck, Lübeck, Germany; Skin Cancer Unit, German Cancer Research Center (DKFZ) and Univ Medical Ho, Mannheim, Germany; Department of Dermatology, Saarland University Medical Center, Homburg/Saar, Germany; Medical Center Quedlinburg, Quedlinburg, Germany; St. Elisabeth Hospital, Oberhausen, University Witten/Herdecke, Oberhausen, Germany; Elbe Kliniken Buxtehude, Buxtehude, Germany; Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany; Department of Dermatology, University Hospital Dresden, Dresden, Germany; Klinikum Ludwigshafen, Ludwigshafen, Germany; University Hospital Essen, Essen, Germany; Department of Dermatology University Essen, Essen, Germany; Essen University Hospital, Essen, Germany; Translational Skin Cancer Research, Deutsches Konsortium für Translationale Krebsforschung (DKTK), Essen, Germany; University Department of Dermatology, Kiel, Germany; Department of Dermatology, University of Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany

Background: PD-1 checkpoint inhibition (CPI) has recently advanced to one of the most effective treatment strategies in melanoma. However, since a considerable proportion of patients shows upfront therapy resistance, baseline predictive biomarkers of therapy outcome are needed. **Methods:** This prospective multicenter study included metastatic melanoma patients whose formalin-fixed paraffin-embedded tumor tissue samples taken prior to the start of a systemic non-adjuvant therapy of any line were analyzed for PD-L1 expression on tumor cells by immunohistochemistry (clone 28-8, DAKO) and for COSMIC-annotated oncogenic mutations by 29-gene panel sequencing (MiSeq, Illumina). Clinical baseline and follow-up data were collected within the DeCOG multicenter skin cancer registry ADOREG. **Results:** From 09/2015 until 10/2020, 706 enrolled patients from 15 centers were evaluable for the endpoints best overall response (BOR), progression-free (PFS) and overall survival (OS). Thereof, 540 patients received PD-1-based CPI as first systemic treatment after tumor tissue analysis. 197/540 patients tested positive for PD-L1 (cut-off = 5%) in pre-treatment tumors, and revealed a favourable BOR (objective response 34.4% versus 19.1%; $p < 0.0001$), PFS (median 10.4 versus 4.2 months; $p < 0.0001$) and OS (median 45.1 versus 18.8 months; $p = 0.001$) compared to patients with PD-L1 negative tumors. 47/540 patients presented oncogenic mutations of three or more genes in pre-treatment tumors, and revealed a favourable BOR (objective response 46.8% versus 32.1%; $p = 0.041$), PFS (median 15.1 versus 6.1 months; $p = 0.008$) and OS (median not reached versus 25.2 months; $p = 0.027$) compared to patients whose tumors showed mutations in two or less genes. Multivariable Cox regression including sex, primary site, non-adjuvant systemic pre-treatment, serum LDH, and ECOG performance state demonstrated tumor PD-L1 expression and gene panel mutational profile as independent predictors of survival upon treatment with PD-1-based CPI. In contrast, in 106/706 patients treated with BRAF/MEK inhibitors as first systemic treatment after tumor tissue analysis, no association was found between tumor PD-L1 expression or gene panel mutational profile and therapy outcome. **Conclusions:** PD-L1 expression quantification and gene panel mutational profiling provide useful outcome predictors of PD-1-based CPI therapy in metastatic melanoma patients. Research Sponsor: Bristol Myers Squibb, Dermatologic Oncology Group (DeCOG).

9569 **Poster Session**

Analysis of patients (pts) with in-transit metastases treated with nivolumab (NIVO) or ipilimumab (IPI) in CheckMate 238.

James Larkin, Helen Gogas, Michele Del Vecchio, Michele Maio, Petr Arenberger, Ana Maria Arance, Jean-Jacques Grob, Vanna Chiarion-Sileni, Karl D. Lewis, Laurent Mortier, Patrick Alexander Ott, Georgina V. Long, Alfonsus Van Den Eertwegh, C. Lance Cowey, Michael Schenker, Marcus O. Butler, Maurice Lobo, Margarita Askelson, Paolo Antonio Ascierto, Jeffrey S. Weber; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; National and Kapodistrian University of Athens, Athens, Greece; Head, Unit of Melanoma Medical Oncology Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; Department of Dermatology, Charles University Third Faculty of Medicine and University Hospital Kralovske Vinohrady, Prague, Czech Republic; Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Aix-Marseille University, CHU Timone, Marseille, France; Head of Melanoma Cancer Unit, Melanoma Oncology Unit, Veneto Institute of Oncology IOV–IRCCS, Padua, Italy; University of Colorado Comprehensive Cancer Center, Aurora, CO; Universite Lille, Centre Hospitalier Regional Universitaire de Lille, Lille, France; Dana-Farber Cancer Institute, Boston, MA; Professor of Melanoma Medical Oncology and Translational Research, Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, North Sydney, Australia; Amsterdam University Medical Center, VUMC, Amsterdam, Netherlands; Medical Oncology, Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Oncology Center, Oncology Center Sf Nectarie Ltd., Craiova, Romania; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Bristol Myers Squibb, Princeton, NJ; Biostatistics, Bristol Myers Squibb, Princeton, NJ; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: In the phase 3 CheckMate 238 study, NIVO has demonstrated improved recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) vs IPI in pts with resected stage IIIB–C or IV melanoma, which was sustained at the 4-y analysis. Having in-transit metastases/satellites (ITM) is a poor prognostic factor, and pts with ITM are generally omitted from clinical trials. This study was the first and only adjuvant checkpoint inhibitor trial to include pts with ITM. Here, we present post hoc outcomes in this subgroup. **Methods:** Pts aged ≥15 y with completely resected stage IIIB–C or IV melanoma stratified by stage and tumor PD-L1 status were 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 a maximum of 1 y or until disease recurrence/unacceptable toxicity. Pts with ITM, with or without synchronous nodal involvement, were included. The primary study endpoint was RFS; overall survival (OS) was a secondary endpoint; and DMFS was exploratory. **Results:** Each of the 2 treatment groups had 164 pts with ITM. Baseline characteristics were generally similar between treatment groups in pts with or without ITM; in pts with ITM vs without ITM, tumor ulceration was less frequent in NIVO-treated pts, and fewer IPI-treated pts had PD-L1 expression ≥5%. RFS and DMFS favored NIVO vs IPI in all ITM subgroups (table). OS was similar to the intention-to-treat (ITT) population with no differences noted between treatment groups or between ITM subgroups. Among pts with or without ITM, dominant metastatic sites were lung and lymph nodes, followed by brain, liver, and soft tissue (in varying order). Similar metastasis patterns were observed in pts with ITM regardless of nodal involvement. Treatment-related adverse events (any grade and grade 3/4) in pts with ITM were similar to those of the ITT population. **Conclusions:** Results of this post hoc 4-y analysis of CheckMate 238 showed that safety and efficacy were similar in pts with or without ITM, supporting the use of adjuvant NIVO in pts with ITM, regardless of nodal involvement. Clinical trial information: NCT02388906. Research Sponsor: Bristol Myers Squibb, Pharmaceutical/Biotech Company.

	No ITM	No ITM	ITM	ITM	ITM with nodes	ITM with nodes	ITM, no nodes	ITM, no nodes
Treatment	NIVO (n = 206)	IPI (n = 202)	NIVO (n = 164)	IPI (n = 164)	NIVO (n = 83)	IPI (n = 90)	NIVO (n = 81)	IPI (n = 74)
4-y RFS, % (95% CI)	54 (47–61)	46 (38–52)	50 (42–58)	38 (30–45)	53 (41–63)	35 (24–45)	49 (37–59)	41 (29–52)
HR (95% CI)	0.77 (0.58–1.02)	—	0.63 (0.47–0.86)	—	0.57 (0.37–0.87)	—	0.72 (0.47–1.12)	—
4-y DMFS, % (95% CI)	60 (53–67)	53 (46–60)	58 (49–65)	53 (45–61)	59 (47–69)	51 (39–62)	56 (43–66)	56 (44–67)
HR (95% CI)	0.79 (0.58–1.07)	—	0.79 (0.56–1.11)	—	0.71 (0.44–1.14)	—	0.90 (0.55–1.49)	—
4-y OS, % (95% CI)	76 (69–81)	75 (68–81)	79 (72–85)	79 (72–85)	78 (67–86)	77 (67–85)	81 (70–88)	82 (70–89)
HR (95% CI)	0.93 (0.63–1.36)	—	0.89 (0.55–1.43)	—	0.81 (0.42–1.54)	—	1.03 (0.50–2.11)	—

9570 **Poster Session**

A phase Ib clinical trial of neoadjuvant OrienX010, an oncolytic virus, in combination with toripalimab in patients with resectable stage IIIb to stage IVM1a acral melanoma.

Xuan Wang, Chuanliang Cui, Lu Si, Caili Li, Jie Dai, Lili Mao, Xue Bai, Zhihong Chi, Xinan Sheng, Yan Kong, Bin Lian, Bixia Tang, Xieqiao Yan, Li Zhou, Siming Li, Robert H.I. Andtbacka, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: Metastatic acral melanoma is very difficult to treat. Unlike cutaneous melanoma, acral melanoma responds poorly to checkpoint inhibitors in monotherapy. OrienX010 is a granulocyte-macrophage colony-stimulating factor expressing herpes simplex type-1 derived oncolytic virus. It has shown robust efficacy in metastatic acral melanoma, and may improve the response to checkpoint inhibitors. To evaluate the role of OrienX010 in combination with checkpoint inhibitors in acral melanoma, we conducted a Phase Ib neoadjuvant trial of OrienX010 in combination with the anti-PD-1 monoclonal antibody toripalimab in resectable stage IIIB-IVM1a acral melanoma (NCT04197882). **Methods:** Patients with resectable stage IIIB-IV M1a acral melanoma received neoadjuvant intratumoral OrienX010 up to 10 mL of 8 x 10^7 pfu/mL and intravenous toripalimab 3 mg/kg every 2 weeks for 4 – 6 doses prior to surgical resection. After resection, adjuvant toripalimab 3 mg/kg was administered every 3 weeks for up to 1 year. The primary endpoints were radiographic response rate per RECIST 1.1 and pathological response rate (pCR and pPR). The secondary endpoints were 1- and 2-year recurrence-free survival, and safety. **Results:** Between July 2019 and Jan 2021, 30 patients with regional metastatic acral melanoma were enrolled. Median age was 56.5 years, 14 (47%) were male, 19 (63%) had recurrent disease, and stage IIIB 12 (40%), IIIC 14 (47%), and IVM1a 4 (13%). Median tumor burden was 28mm (range, 10-80mm), and only 5 (17%) patients had melanoma mutations (2 cKIT, 1 NRAS, 2 BRAF). To date, of 24 patients who completed neoadjuvant treatment, 21 (88%) underwent surgery. Three (12%) patients did not undergo surgery due to disease progression prior to surgery and 6 patients are still receiving neoadjuvant treatment. Radiographic responses were seen in 10 (33%) patients. However, 17 of 21 (81%) patients showed pathologic responses in resected metastases, with 3 (14%) showing a pCR and 14 (67%) a pPR. Pathologic responses were associated with greater lymphoid infiltrate, hyaline fibrosis, and decrease in Ki-67 expression in the metastasis. At a median follow-up of 8.9 months, none of the patients who underwent resection have recurred. The neoadjuvant treatment was well tolerated, with all patients experiencing at least 1 treatment related adverse event (TRAE) and Grade 1 fever was most common. Three (10%) patients had a grade 3-4 TRAE, including 1 alanine aminotransferase increase and 2 wound infections. **Conclusions:** Neoadjuvant treatment with OrienX010 and toripalimab in resectable stage IIIB-IVM1a acral melanoma was well tolerated and produced a high pathologic response rate. To date, no patients have recurred, and recurrence-free survival evaluation is ongoing. This combination therapy warrants further evaluation in acral melanoma. Clinical trial information: NCT04197882. Research Sponsor: Oriengene Biotechnology Ltd.

9571 **Poster Session**

Management of resected stage III/IV melanoma with adjuvant immunotherapy.

Rebecca Johnson, Victoria Atkinson, Prachi Bhave, Alison Margaret Weppler, Geoffrey David Peters, Afaf Abed, Megan Lyle, Muhammad Adnan Khattak, Andrew Mark Haydon, Matteo S. Carlino, Shahneen Kaur Sandhu, Georgina V. Long, Alexander M. Menzies; Melanoma Institute Australia, Sydney, Australia; Princess Alexandra Hospital, Greenslopes Private Hospital and University of Queensland, Brisbane, Australia; Westmead Hospital, Sydney, NSW, Australia; Peter MacCallum Cancer Centre, Melbourne, Australia; The Canberra Hospital, Canberra, Australia; Linear Clinical Research, Nedlands, WA, Australia; Liz Plummer Cancer Centre, Cairns and Hinterland Hospital and Health Service, Cairns, QLD, Australia; Royal Perth Hospital, Western Australia, Australia; The Alfred Hospital, Melbourne, VIC, Australia; Peter MacCallum Cancer Center, Melbourne, VIC, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, Mater Hospital and Royal North Shore Hospital, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia

Background: Adjuvant anti-PD1 therapy reduces the risk of recurrence in resected stage III/IV melanoma and is now standard care. Limited data exist beyond registration trials. We sought to explore the use of adjuvant immunotherapy in routine clinical practice. **Methods:** Patients (pts) from 11 Australian centres who received adjuvant nivolumab (nivo) for resected stage III/IV melanoma were included in this study. Efficacy, toxicity, surveillance, recurrence characteristics, management and further treatment outcomes were examined. **Results:** 471 pts received adjuvant nivo between 8/2018 to 3/2020. 318 (68%) were male, median age 64y (range 17-94), 28 (6%) were AJCC v8 IIIA, 194 (41%) IIIB, 175 (37%) IIIC, 11 (2%) IIID, and 63 (13%) IV. 65 (14%) pts had in-transit only disease, 152 (37%) pts were sentinel lymph node biopsy (SLNB+) and only 9 (6%) of these had CLND. 128 (27%) had BRAF mutant (BRAFmt) melanoma. Median time from resection to start of adjuvant nivo was 1.8 months (mo) (range 0.2-4.0). Median FU was 17.5 mo. 256 (54%) pts completed 12 months of nivo, 86 (18%) ceased early for toxicity, 76 (16%) for disease recurrence, 25 (5%) other reasons (COVID-19 8, co-morbidities 7, pt choice 10); 28 (6%) pts were still receiving nivo at data cut. Median duration of treatment was 10.4 mo (range 0-16.8). 117 (25%) pts recurred; 76 (65%) while ON nivo and 41 (35%) OFF nivo ($>$ 1 month after last dose, including 20 pts who stopped early for toxicity). 24 mo RFS was 69%. Median time to recurrence was 6.0 mo (95% CI 5.1, 7.5). 56 (48%) had first recurrence with locoregional (LR) disease only and 61 (52%) had distant +/- LR recurrence. Of those who recurred with LR disease only, 46/56 (82%) underwent surgery, 15/46 (33%) then had adjuvant radiotherapy, and 15/46 (33%) had 'second adjuvant' therapy with BRAF/MEK inhibitors (15/21, 71% BRAFmt pts). 10/56 (37%) pts who recurred with LR disease subsequently recurred distantly. 58/80 (73%) pts received systemic therapy at either 1st or subsequent unresectable recurrence. For recurrences ON nivo, 18 pts received combination ipilimumab (ipi) and nivo (ORR 44%), 4 pts had ipi monotherapy (ORR 0%), 7 pts had anti-PD1 + investigational agent (ORR 57%), 11 pts had BRAF/MEK inhibitors (ORR 82%). 1 pt had PD with ongoing PD1 monotherapy. For recurrences OFF nivo, no patients responded to PD1 alone (n = 1) or with an investigational agent (n = 1), ipi+nivo (n = 3), ipi monotherapy (n = 4) or chemotherapy (n = 2); 6 pts received BRAF/MEK inhibitors (ORR 50%). 2-year OS was 92%. **Conclusions:** Despite higher rates of discontinuation due to toxicity compared with clinical trial cohorts, the efficacy data appear similar. Most early recurrences are distant, and many with LR recurrence soon recur distantly thereafter. Second line adjuvant BRAF/MEK inhibitors are frequently used for resected LR recurrence. Both ipi+nivo and BRAF/MEK inhibitors appear to have activity after distant recurrence. Research Sponsor: None.

9572 **Poster Session**

Propensity weighted indirect treatment comparison of nivolumab (NIVO) versus placebo (PBO) as adjuvant therapy for resected melanoma: A number needed to treat and overall survival analysis.

Jeffrey S. Weber, Tayla Poretta, Brian Stwalley, Leon Sakkal, Ella X. Du, Travis Wang, Yan Chen, Yan Wang, Keith A. Betts, Alexander Noor Shoushtari; Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY; Bristol Myers Squibb, Lawrenceville, NJ; Bristol Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Lawrenceville, NJ; Analysis Group, Inc, Los Angeles, CA; Analysis Group, Inc., Boston, MA; Analysis Group, Inc., Los Angeles, CA; Memorial Sloan Kettering Cancer Center, New York, NY

Background: The CheckMate 238 trial demonstrated that NIVO improved recurrence free survival (RFS) vs. ipilimumab (IPI). The EORTC 18071 trial demonstrated that IPI improved RFS and overall survival (OS) vs. PBO. The current study pooled data from these two trials to indirectly assess the RFS and OS of NIVO vs. PBO and the numbers needed to treat (NNTs) for one additional recurrence-free survivor and survivor over 4 years. **Methods:** Patients with resected AJCC 7th edition stage IIIB/C cutaneous melanoma from CheckMate 238 (NIVO vs. IPI) and EORTC 18071 (IPI vs. PBO) were pooled together with inverse probability weighting to balance between-trial differences in baseline characteristics. NNTs were calculated for RFS and OS comparing NIVO vs. IPI and PBO over 4 years. To account for improved post-recurrence survival over time, a sensitivity analysis that adjusted for post-recurrence survival in the PBO arm of EORTC 18071 was performed. **Results:** A total of 278, 643, and 365 patients treated with NIVO, IPI, and PBO, respectively, were included. In the weighted samples, patients treated with NIVO had consistently higher RFS rates than those treated with IPI (HR [95% CI]: 0.69 [0.56, 0.85]) and PBO (HR: 0.49 [0.39, 0.61]). NIVO was associated with similar OS as IPI (HR: 0.80 [0.60, 1.08]) and superior OS compared to PBO (HR: 0.45 [0.33, 0.60]). At 4 years, the weighted RFS rate was 53.1% for NIVO, 41.8% for IPI, and 29.1% for PBO. The NNT to achieve one additional recurrence-free survivor was 4.2 for NIVO vs. PBO and 8.9 for NIVO vs. IPI. The NNT to obtain one additional survivor was 4.8 for NIVO vs. PBO and 22.2 for NIVO vs. IPI. The OS rate for PBO after adjusting for differences in post-recurrence treatments at 4 years was 64.1%, and the corresponding NNT of OS comparing NIVO vs. adjusted PBO was 8.5. **Conclusions:** In patients with resected AJCC 7th edition stage IIIB/C cutaneous melanoma, this indirect comparison showed that NIVO improved RFS and OS vs placebo, with OS improvement maintained after adjustment for post-recurrence therapy. Research Sponsor: Bristol Myers Squibb.

NNT in patients with resected stage IIIB/C cutaneous melanoma.

	RFS rate			RFS NNT (95% CI)		OS rate				OS NNT (95% CI)		OS NNT (95% CI) - sensitivity analysis
Follow-up time (years)	NIVO	IPI	PBO	NIVO vs. PBO	NIVO vs. IPI	NIVO	IPI	PBO	Adjusted PBO	NIVO vs. PBO	NIVO vs. IPI	NIVO vs. adjusted PBO
1	73.1%	61.1%	48.9%	4.1 (3.1, 6.1)	8.3 (5.3, 19.2)	97.6%	93.0%	84.9%	87.9%	7.9 (5.9, 11.9)	21.6 (13.5, 53.7)	10.4 (5.4, 104.1)
2	65.2%	50.8%	38.5%	3.7 (2.9, 5.3)	6.9 (4.6, 13.9)	88.4%	84.0%	70.5%	74.3%	5.6 (4.1, 8.8)	22.6 (-131.1 to 10.4)	7.1 (4.0, 22.9)
3	60.2%	44.7%	30.9%	3.4 (2.7, 4.7)	6.5 (4.4, 12.5)	81.8%	76.8%	59.8%	67.1%	4.6 (3.4, 6.8)	20.3 (-92.8 to 9.1)	6.8 (3.9, 29.0)
4	53.1%	41.8%	29.1%	4.2 (3.1, 6.3)	8.9 (5.3, 27.4)	75.8%	71.3%	55.0%	64.1%	4.8 (3.5, 7.7)	22.2 (-45.0 to 8.9)	8.5 (4.3, 771.8)

9573 **Poster Session**

Adjuvant anti-PD-1 ab (Toripalimab) versus high-dose IFN-a2b in resected mucosal melanoma: A phase randomized trial.

Chuanliang Cui, Bin Lian, Lu Si, Zhihong Chi, Xinan Sheng, Yan Kong, Xuan Wang, Hui Tian, Lili Mao, Xue Bai, Bixia Tang, Xieqiao Yan, Siming Li, Li Zhou, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China; Peking University Cancer Hospital and Institute, Beijing, China; Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: Immunotherapies including anti PD-1 ab and high-dose IFN-a2b (HDI) have been approved for adjuvant therapies in resected cutaneous melanoma, but their roles in mucosal melanoma are still unknown. To determine the efficacies of toripalimab versus HDI as adjuvant therapy in patients (pts) with resected mucosal melanoma, this open-label, phase randomized trial was conducted. **Methods:** Mucosal melanoma pts who have undergone complete resections of localized with or without regional lymphatic disease were randomly (1:1) assigned to receive HDI ($15x10^6$ IU/m^2/d1-5/w/ 4weeks IH, followed by $9x10^6$ IU tiw IH) or toripalimab (3mg/kg intravenously q2w) for 52 weeks unless disease recurrence, unacceptable toxicity or consent withdrawal. Head and neck primary would receive adjuvant radiotherapy within 6-8weeks after enrollment. The primary end point was RFS in the intention-to-treat population. Data cutoff was December 10, 2020. Clinical trial information: NCT03178123. **Results:** From Jul 2017 to May 2019, 187 pts were screened, and 145 were randomized into HDI group (n = 72) and toripalimab group (n = 73). The median age was 58years; M:F 37.2%: 62.8%; localized disease 80.7%, regional lymphatic disease 19.3%; local excision ± CLND 37.2%, wide excision ± CLND 62.8%; head and neck primary 39.3%(87.5% received adjuvant radiotherapy); PDL-1positive 51.0%(CPS≥1%, 22C3), PDL-1 negative 49.0%. There was no difference in baseline characteristics between two groups. At a median follow-up of 31.5 months, there were 93 RFS events (43 in HDI group vs. 50 in toripalimab group), 76 DMFS events (35 vs. 41respectively) and 65 OS events (30 vs. 35 respectively). The median RFS, DMFS and OS were shown in the table. In the HDI group, 32.6% of pts received anti PD-1 ab in the following treatment. Grade 3/4 AEs were reported in 83.3% of pts in HDI group (most decrease of leukocytes or neutrophils) and 15.1% of pts in toripalimab group (mainly increase of amylase or liver enzymes). Discontinuations of treatment due to any AE occurred in 20.8% of HDI group and 15.1% of toripalimab group. **Conclusions:** Both adjuvant toripalimab and HDI therapy improve RFS of mucosal melanoma. Toripalimab shows longer RFS in PDL1 (+) subgroup and better tolerance than HDI. Clinical trial information: NCT03178123. Research Sponsor: Shanghai Junshi biosciences Co.

	Total		PDL1+		PDL1-	
	HD-IFN (N = 72)	PD-1 (N = 73)	HD-IFN (N = 36)	PD-1 (N = 38)	HD-IFN (N = 36)	PD-1 (N = 35)
Median RFS, mo.(95% CI)	13.9 (8.3-21.3)	13.6 (8.3-18.0)	11.1 (5.7-21.3)	17.3 (8.2-22.9)	14.6 (5.7-21.3)	11.3 (5.6-18.0)
HR (95% CI)	1.06 (0.69-1.63)		0.94 (0.53-1.65)		1.06 (0.59-1.90)	
Median DMFS, mo.(95% CI)	14.6 (8.3-21.3)	14.4 (9.7-21.4)	11.1 (6.6-21.3)	17.8 (9.3-24.3)	17.4 (8.3-21.8)	12.7 (8.3-18.0)
HR (95% CI)	0.98 (0.63-1.52)		0.81 (0.45-1.44)		1.03 (0.57-1.88)	
Median OS, mo.(95% CI)	NR (31.2-NR)	NR (28.1-NR)	NR (16.2-NR)	32．9 (22.9-NR)	NR (26.2-NR)	NR (24.7-NR)
HR (95% CI)	1.08 (0.64-1.85)		0.99 (0.49-1.98)		1.18 (0.53-2.64)	

9574 **Poster Session**

Association of health-related quality of life (HRQoL) and treatment safety with nivolumab (NIVO) in patients (pts) with resected stage IIIB/C or IV melanoma: Analysis of CheckMate 238 four-year follow-up (FU) data.

Jeffrey S. Weber, Helen Gogas, Xiaowu Sun, Christine Yip, Fiona Taylor, Julia Braverman, Maurice Lobo, Pratik K. Thakkar, Andriy Moshyk, James Larkin, Paolo Antonio Ascierto; Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY; National and Kapodistrian University of Athens, Athens, Greece; Adelphi Values, Boston, MA; Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Uxbridge, United Kingdom; Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy

Background: In CheckMate 238, NIVO 3 mg/kg vs ipilimumab 10 mg/kg showed significantly longer recurrence-free survival and a lower rate of grade 3–4 treatment-related adverse events (TRAEs) in pts with completely resected stage IIIB/C or IV melanoma. This analysis assessed the association of long-term HRQoL and TRAEs in NIVO-treated pts in this trial. **Methods:** HRQoL was assessed using EORTC QLQ-C30 (global health status [GHS] and physical/emotional functioning) and EQ-5D-3L visual analogue scale (VAS) questionnaires administered after randomization, during 1 y of treatment (wk 5, 7, 11, 17, 25, 37, and 49), at posttreatment FU visits 1 and 2 (FU1 and FU2; 30 and 114 days after last dose), and at survival FU visits up to 4 y after last dose (EQ-5D-3L only). NIVO-treated pts were grouped based on whether they had experienced a grade 3–4 TRAE, any-grade TRAE leading to NIVO discontinuation, or any-grade select (immune-related) TRAE on treatment or up to 100 days after last dose. Longitudinal change from baseline (BL) in scores was assessed for pts with and without TRAEs having patient-reported outcome data at BL and ≥1 post-BL assessment (HRQoL population) using descriptive statistics. QLQ-C30 subscale and VAS changes of 10 and 7, respectively, were considered clinically meaningful. **Results:** The HRQoL population comprised 446 of 453 pts randomized to NIVO. EQ-5D-3L assessments were completed by 81% of survivors (263/324) after 4 y post-randomization. Grade 3–4 TRAEs occurred in 17% of NIVO-treated pts (77/446). A slight trend toward deterioration of GHS from BL on treatment was noted, with clinically meaningful deterioration at posttreatment FU1 (mean [SD], −13.8 [25.0]) and FU2 (−10.3 [22.0]; last available time point). For the VAS, a similar trend on treatment was noted (−6.9 [28.3] at wk 11), with a clinically meaningful deterioration after NIVO discontinuation (−9.9 [27.0] at FU1) and a return to BL level by the start of survival FU. For pts without grade 3–4 TRAEs, mean change from BL scores remained stable (ie, no clinically meaningful deterioration on treatment or during FU). Any-grade TRAEs led to NIVO discontinuation in 9% of pts (42/446); HRQoL findings were similar to those for pts with grade 3–4 TRAEs. The most common any-grade TRAE was fatigue (35%). No clinically meaningful deterioration in VAS was noted for any select TRAE during FU except for hyperthyroidism (8%), with which deterioration occurred at FU1. EORTC QLQ-C30 physical and emotional functioning results will be presented. **Conclusions:** In CheckMate 238, pts with TRAEs showed early HRQoL deterioration after NIVO discontinuation, but HRQoL returned to BL levels with no sustained deterioration during survival FU. Overall, HRQoL was maintained on treatment and over a long-term FU period in pts with resected melanoma receiving adjuvant NIVO. Clinical trial information: NCT02388906. Research Sponsor: Bristol Myers Squibb.

9575 **Poster Session**

Postoperative radiotherapy in Merkel cell carcinoma (MCC).

Sonja Levy, Stephanie Blankenstein, Dirk J. Grunhagen, Mathilde Jalving, Olga Hamming-Vrieze, Lukas B. Been, Lisa Tans, Alexander Christopher Jonathan Van Akkooi, Margot Et Tesselaar; Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; University Medical Center Groningen, Groningen, Netherlands; Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Surgical Oncology, University Medical Center Groningen, Groningen, Netherlands; Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Rotterdam, Netherlands

Background: MCC is a rare and aggressive neuroendocrine malignancy of the skin. Postoperative radiotherapy (PORT) is recommended by current guidelines to reduce recurrences and improve survival in patients with locoregional MCC. However, evidence supporting these recommendations is conflicting and deviations from the protocol occur frequently, due to the generally elderly and frail patient population. We aim to evaluate the influence of PORT on survival in stage I-III MCC patients treated in the Netherlands. **Methods:** All patients with stage I-III MCC treated in three referral centers between 2013 and 2018 were included retrospectively. Recurrence free survival (RFS) and disease specific survival (DSS, including death from unknown causes) were compared between patients with and without PORT. Prognostic factors for DSS were analyzed using Kaplan-Meier curves, logrank test and cox regression. Since sentinel node biopsies (SN) are frequently omitted in this patient population, analyses were performed in patients with clinical (SN not performed) stage I/II (c-I/II-MCC), pathologic (SN negative) stage I/II (p-I/II-MCC) and stage III MCC (III-MCC), separately. Propensity score matching (PSM) was performed to assess possible confounding by indication. **Results:** In total 219 patients were included, of whom 54 had p-I/II-MCC, 82 had c-I/II-MCC and 83 had III-MCC. Median follow up time was 53.4 (IQR 32.8-62.4), 28 (11.8-43.3) and 30.8 (19.5-50.0) months, respectively. PSM identified no confounding by indication, analyses were therefore performed in the unmatched cohort. Majority of recurrences were regional in p-I/II-MCC (77.8%) and c-I/II-MCC (74.2%), and distant in III-MCC (61.7%). RFS was significantly different across all stages ($p<0.001$), DSS was similar for patients with c-I/II-MCC and III-MCC, which was significantly worse compared to patients with p-I/II-MCC (p=0.003). Survival times are shown in table. PORT did not improve RFS and DSS in patients with p-I/II-MCC and c-I/II-MCC. In patients with III-MCC, PORT was associated with improved RFS, but not with DSS. Multivariable analysis identified male gender (hazard ratio (HR) 1.94, p=0.030), performance status (PS) of 3 (HR 3.87, p=0.014) and an unknown PS (HR 5.45, p=0.004), primary tumor on the trunk (HR 2.67, p=0.008), c-I/II-MCC (HR 5.38, p=0.001) and III-MCC (HR 6.44, $p<0.001$) as predictors for DSS. Effect of PORT was not significant. **Conclusions:** In this retrospective cohort PORT did not show a DSS benefit in patients with stage I-III MCC. RFS was improved by PORT in III-MCC. PSM showed no confounding by indication. Research Sponsor: None.

		# patients	1 yr RFS	2 yr RFS	5 yr RFS	p	1 yr DSS	2 yr DSS	5 yr DSS	p
p-I/II-MCC	All	54				0.505				0.647
	No PORT	42	98%	87%	81%		100%	95%	82%	
	PORT	12	92%	92%	92%		100%	100%	100%	
c-I/II-MCC	All	82				0.343				0.132
	No PORT	50	70%	51%	51%		84%	68%	50%	
	PORT	32	80%	59%	59%		97%	83%	69%	
III-MCC	All	83				0.021				0.978
	No PORT	36	49%	30%	30%		97%	78%	63%	
	PORT	47	76%	48%	48%		98%	76%	62%	

RFS and DSS, logrank test for comparison.

9576 **Poster Session**

Isolated same-basin lymph node recurrence after precision lymph node excision for clinically evident melanoma metastasis.

Kevin Lynch, Yinin Hu, Norma Farrow, Yun Song, Max Meneveau, Minyoung Kwak, Michael C. Lowe, Edmund Bartlett, Georgia Beasley, Giorgos Karakousis, Craig L. Slingluff; University of Virginia Health System, Charlottesville, VA; University of Maryland, Baltimore, MD; Duke University, Durham, NC; University of Pennsylvania Health System, Philadelphia, PA; SUNY Downstate, Brooklyn, NY; Department of Surgery, Emory University, Atlanta, GA; Memorial Sloan-Kettering Cancer Center - Fellowship (GME Office), New York, NY; Hospital of the University of Pennsylvania, Philadelphia, PA; University of Virginia School of Medicine, Charlottesville, VA

Background: While management of the nodal basin for melanoma has largely moved to observation for microscopic sentinel lymph node (SLN) metastasis, complete lymph node dissection (CLND) remains the current standard of care for melanoma patients with macroscopic, clinically detectable lymph node metastases (cLN). As CLND is associated with high surgical morbidity, we sought to study whether cLN may be safely managed by excision of only clinically abnormal nodes (precision lymph node dissection, PLND). Currently, a small subset of patients with cLN do not undergo CLND because of frailty or patient preference. We hypothesized that in these selected patients, PLND would provide acceptable regional control rates. **Methods:** Retrospective chart review was conducted at four academic tertiary care hospitals to identify melanoma patients who underwent PLND for cLN. cLN were defined as palpable or radiographically abnormal nodes. Recurrences were categorized as local/in-transit, same-basin lymph node, or distal lymph node/visceral. The primary outcome was isolated same-basin recurrence after PLND. **Results:** Twenty-one patients underwent PLND for cLN without synchronous distant metastases (characteristics of primary lesions summarized in Table). Reasons for forgoing CLND included patient preference (n=8), imaging indeterminate for distant metastases (n=2), comorbidities (n=4), loss to follow up (n=1), partial response to checkpoint blockade (n=1), or not reported (n=5). The inguinal node basin was the most common site (n=10), followed by the axillary (n=8) and cervical basins (n=3). A median of 2 nodes were resected at PLND, and 68% of resected nodes were positive for melanoma (median: 1, range: 1-3 nodes). Median follow-up was 23 months from PLND, and recurrence was observed in 28.6% of patients overall. Only 1 patient (4.8%) developed an isolated same-basin recurrence. The 3-year cumulative incidence of isolated same-basin recurrence was 5.3%, while risk of isolated local/in-transit recurrence or distant basin/visceral metastasis were 19.8% and 33.3%, respectively. Complications from PLND were reported in 1 patient (4.8%) and were limited to post-operative seroma and lymphedema. **Conclusions:** These pilot data suggest that PLND may offer acceptable regional disease control for cLN. Post-operative morbidity from PLND was also low, raising the possibility that PLND may provide adequate regional disease control without the morbidity associated with CLND. These data justify additional, prospective evaluation of PLND in selected patients. Research Sponsor: None.

Primary tumor characteristics.	
Tumor Location	
Upper Extremity	2
Trunk	5
Lower Extremity	4
Anal Canal	1
Unknown Primary	7
Not Reported	2
Tumor Histology	
Breslow Thickness*	3.0 (2.6-7.8)
Perineural/ Lymphovascular Invasion	31%
Ulceration	69%
BRAF Mutant	43%

*Median (IQR). Millimeters (mm).

9577 **Poster Session**

Evaluation of patients with surgically resected high-risk melanoma receiving adjuvant therapy in routine clinical practice in the United States.

Michael B. Atkins, Cristina Julian, Matthew H. Secrest, Janet Lee, Ana Maria Abajo Guijarro, Edward Francis Mckenna; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd., Basel, Switzerland

Background: The management of patients with resected stage III melanoma has changed in recent years, and real-world data on recurrence patterns and adjuvant therapy responses are scarce. This study assessed adjuvant treatment patterns and outcomes in patients with advanced melanoma by *BRAF* status and relapse location. **Methods:** Patients diagnosed with stage III advanced melanoma between January 2011 and February 2020 in the nationwide Flatiron Health electronic health record–derived deidentified database were included if they were ≥18 years, received approved first-line (1L) adjuvant therapy after January 2018 with checkpoint inhibitors (CPIs; eg, nivolumab, pembrolizumab) or targeted therapies (TTs; eg, dabrafenib/trametinib), had 6 months' follow-up and had ≥1 visit after starting adjuvant therapy (Cohort 1). Patients from Cohort 1 were included in Cohort 2 if they had a recurrence following initiation of adjuvant therapy, and those from Cohort 2 were included in Cohort 3 if they had a distant recurrence and available documented *BRAF* status at any time. Time to next systemic treatment (TTNT), overall survival (OS) and relapse free survival (RFS) were estimated using Kaplan-Meier (KM) methods from adjuvant therapy start (Cohort 1), first recurrence date (Cohort 2) or first distant recurrence date (Cohort 3). **Results:** Cohort 1 included 447 patients receiving 1L adjuvant therapy; Cohort 2 included patients after first distant (n = 47) or local (n = 35) relapse; Cohort 3 included distant-recurrent patients with tumors that were *BRAF* wild type (WT) (n = 22) or *BRAF* mutant (n = 23). The majority of patients were aged < 65 years. Across cohorts, relative use of TTs vs CPIs was similar: Cohort 1 (4.5% vs 96%), Cohort 2 (2.4% vs 98%) and Cohort 3 (2.2% vs 98%). Nivolumab was the most frequent treatment used across cohorts (84%-88%). In Cohort 1, 1- and 2-year KM probabilities for OS, RFS and TTNT were 93.5%/83.8%, 83.2%/70.6% and 84.0%/62.4%, respectively. In Cohort 2, for patients with local recurrence, 6- and 12-month OS probabilities were 93.4% and 78.8%, respectively, which were substantially higher than those for patients with distant recurrence (64.5% and 46.9%). In Cohort 3, for patients with documented *BRAF* mutations, 6- and 12-month OS rates from disease recurrence were 79.1% and 49.4%, respectively, which were greater than for those with *BRAF*-WT tumors (54.1% and 46.3%). **Conclusions:** Early RFS and OS outcomes for patients with surgically resected Stage III melanoma appear comparable to those reported in randomized clinical studies. The majority of patients with advanced melanoma, including patients who experienced recurrence, initiated treatment with CPIs. OS rates were numerically greater for Cohort 3 patients with *BRAF*-mutant tumors. Outcomes for patients with distant recurrence after adjuvant therapy remain unfavorable and represent a continued unmet medical need. Research Sponsor: Genentech, Inc.

Efficacy of adjuvant radiotherapy in recurrent melanoma after adjuvant immunotherapy.

Prachi Bhave, Angela M. Hong, Rebecca Johnson, Alexander M. Menzies, Georgina V. Long, Joanna Mangana, Douglas Buckner Johnson, Zeynep Eroglu, Ozgecan Dulgar, Hui-Ling Yeoh, Andrew Mark Haydon, Georg Lodde, Elisabeth Livingstone, Muhammad Adnan Khattak, Katharina C. Kähler, Axel Hauschild, Wei Wang, Matteo S. Carlino; Westmead Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Chris O'Brien Lifehouse, Sydney, NSW, Australia; Melanoma Institute Australia, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; University Hospital Zürich, Zürich, Switzerland; Vanderbilt University Medical Center, Nashville, TN; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; American Society of Clinical Oncology, Istanbul, Turkey; Alfred Health, Melbourne, NSW, Australia; The Alfred Hospital, Melbourne, VIC, Australia; University Hospital Essen, Heidelberg, Germany; Department of Dermatology, University Hospital Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany; Royal Perth Hospital, Western Australia, Australia; Universitats-Hautklinik Kiel, Kiel, Germany; Schleswig-Holstein University Hospital, Kiel, Germany; Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, Australia

Background: Adjuvant (adj) radiotherapy (RT) halves the risk of locoregional (LR) recurrence in patients (pts) with high risk stage III melanoma after lymphadenectomy (CLND), however its role in the adj immunotherapy (IO) era without CLND is unknown. **Methods:** Pts with resected stage III melanoma who received adj IO and recurred with resectable LR only disease were studied. After resection of this 1st recurrence, adj RT may or may not have been administered. Disease characteristics, treatment at relapse and outcomes were examined. **Results:** 71 pts from 9 centres were included. Prior to adj IO, median age was 60y, 59% male, 56% BRAF mutant, 61% stage IIIC (AJCC V8), 52% underwent CLND and 17% had in-transit (IT) only disease. Adj IO included: 90% single agent anti-PD1, 8% ipilimumab-nivolumab (IN) and 1% nivolumab or IN (blinded on trial). Median duration of adj IO was 5 months. 21(30%) pts had high risk stage III disease at diagnosis, per previously established TROG criteria; 3 (4%) received upfront adj RT prior to recurrence. Median time to 1st recurrence was 7 months. 49 (69%) pts recurred during and 22 (31%) after cessation of adj IO. At 1st recurrence, 9 (13%) pts had stage IIIB disease, 55 (77%) IIIC, 7 (10%) IIID and 8 (11%) continued prior adj IO, 31 (44%) commenced therapy and 32 (45%) had no systemic therapy. 24 (34%) pts received adj RT after resection of 1st recurrence and 47 (66%) did not (Table). Adj RT was associated with a reduced risk of any 2nd recurrence (7/24, 29% vs 26/47, 55%, p=0.03) and LR 2nd recurrence (2/24, 8% vs 17/47, 36%, p=0.012). Whilst pts who received adj RT at 1st recurrence were more likely to have LN only disease, extra nodal extension and involved surgical margins, these factors did not significantly affect overall risk of 2nd recurrence on multivariate analysis. Of note, 70% of pts who did not receive adj RT at 1st recurrence had IT only disease, and though this did not significantly affect rate of 2nd recurrence (p=0.19), this likely reflects an inherent selection bias in this study. RT toxicity occurred in 16 (67%) pts, 10 with dermatitis only, and all grade 1 or 2. Median follow up was 22 months. Median recurrence free survival to 2nd recurrence was 23 months for all pts, not reached for those who had adj RT at 1st recurrence and 19 months for those who did not have adj RT (p=0.047). Median overall survival was not reached. **Conclusions:** Whilst adj RT appears to reduce 2nd recurrences, this may have been influenced by an unavoidable selection bias in the data, particularly an imbalance in the percentage of pts with IT disease. Prospective data with larger cohorts is needed to validate our results. Research Sponsor: None.

Patient Characteristics	Adjuvant RT at 1strecurrence N= 24	No adjuvant RT at 1strecurrence N= 47
1st Recurrence		
LR site	-	-
Nodal only	14 (58)	13 (28)
IT only	6 (25)	33 (70)
Nodal and IT	4 (17)	1 (2)
2nd Recurrence		
Total	7 (29)	26 (55)
LR	2 (29)	17 (65)
Within prior RT field	-	-
Yes	2	2
No	0	15
LR site	-	-
Nodal only	0	5
IT only	2	11
Nodal and IT	0	1
Distant	5 (71)	9 (35)

9579 **Poster Session**

The prognostic value of the interferon-gamma (IFNγ) signature in patients with macroscopic stage III melanoma treated with and without adjuvant systemic therapy.

Judith M. Versluis, Stephanie Blankenstein, Petros Dimitriadis, Joyce Sanders, Willem Hoefakker, Annegien Broeks, Winan J. van Houdt, Yvonne M. Schrage, Michel W.J.M. Wouters, Alexander Christopher Jonathan Van Akkooi, Christian U. Blank; Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Division of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands; Core Facility Molecular Pathology and Biobanking, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Recently, trials have shown the benefit of adjuvant aPD-1 therapy in macroscopic stage III melanoma patients. This treatment has been incorporated in daily clinical practice, however, a substantial part of patients still does not benefit from this therapy, as they develop recurrences. The aim of this study is to evaluate the results of adjuvant aPD-1 therapy and the potency of the IFNγ signature as a prognostic or predictive marker, as it has proven to be predictive of response in neoadjuvant trials. **Methods:** Patients participating in an ongoing biobank study and naïve for systemic therapy were included, between 10-2017 and 06-2020, after complete resection of macroscopic stage III melanoma. Approval and reimbursement of adjuvant therapy in the Netherlands started in 12-2018, resulting in 2 cohorts of similar high risk patients: prior to availability of adjuvant aPD-1 (cohort A) and thereafter (cohort B). Data cut-off for clinical data was January 1st 2021. Transcriptome sequencing was performed on samples of stage III melanoma by CeGaT GmbH, IFNγ signature was determined on these data with the median as cut-off. Clinical data were compared between cohort A and B as intention-to-treat population, including patients with a recurrence before adjuvant therapy start (n=10). **Results:** In total, 99 patients were included: 50 in cohort A and 49 in cohort B. Majority of included patients had thick primary melanomas (Breslow $>$2mm in 59.6%) and stage IIIC/IIID disease (83.3%) according to AJCC 8th edition. At a median follow-up of 20.6 months (95% confidence interval [CI] 16.6-24.7), median recurrence-free survival (RFS) was 6.1 months (95%CI 3.9-8.4) versus 22.8 months (95%CI 8.7-36.9), significantly in favor of cohort B (p=0.011). Median overall survival (OS) was not reached in both patient groups, but was overall significantly different (p=0.040), favoring cohort B. RNA sequencing was performed in 25 patients who received adjuvant therapy and in 24 who did not, excluding patients with an early recurrence ($<$12 weeks). In both treatment groups median (p=0.003) and 12-months RFS (p$<$0.001) was significantly higher for IFNγ high patients, but both IFNγ low and high patients show higher RFS rates when receiving adjuvant aPD-1 therapy (Table). **Conclusions:** Our study confirms RFS and OS benefit of adjuvant aPD-1 for patients with macroscopic stage III melanoma. IFNγ has shown to be a prognostic marker in both patients who were and were not treated with adjuvant therapy, as both patients with IFNγ high and low signatures show benefit from adjuvant therapy. Research Sponsor: None.

		Median RFS (months)	12-months RFS
No adjuvant therapy	IFNγ low	2.8 (95%CI 2.0-3.6)	6.9% (95%CI 0.0-20.3)
	IFNγ high	13.0 (95%CI 3.1-23.0)	53.3% (95%CI 27.5-79.1)
Adjuvant therapy	IFNγ low	5.1 (95%CI 0.0-12.1)	40.3%(95%CI 16.1-64.5)
	IFNγ high	18.6 (95%CI 12.1-25.1)	70.1% (95%CI 47.7-92.5)

9580 **Poster Session**

Incidence, timing, and predictors of CNS metastasis in patients (Pts) with clinically localized cutaneous melanoma (CM).

Merve Hasanov, Denai R. Milton, Sapna Pradyuman Patel, Hussein Abdul-Hassan Tawbi, Isabella Claudia Glitza, Sherise D. Ferguson, Debora Alexandra Ledesma, Carlos A. Torres-Cabala, Alexander J. Lazar, Elizabeth M. Burton, Jeffrey E. Gershenwald, Lauren Elaine Haydu, Michael A. Davies; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Surveillance for CNS metastasis (mets) is not routinely performed in pts with clinically localized CM. Improved understanding of the incidence, timing and risk factors for the development of CNS metastasis in these pts may inform surveillance strategies. **Methods:** Under an IRB-approved protocol, demographics, tumor characteristics, and clinical events were collected for pts diagnosed from 1998 to 2019 with AJCC 8th edition stage I or II CM at MD Anderson Cancer Center. Dates of initial diagnosis, regional, distant non-CNS, and CNS mets were recorded. Symptoms and the extent of disease (brain, LMD, both) were recorded for pts with CNS mets. Cumulative incidence of distant mets (CNS and non-CNS) was determined using the competing risks method, including death; pts without CNS mets and alive at last follow-up were censored. Differences in cumulative incidence between groups were assessed using Gray's test. Associations between measures of interest and cumulative incidence were determined using proportional subdistribution hazards regression models. All statistical tests used a significance level of 5%. **Results:** 5,179 Stage I-II CM pts were identified. At a median follow up of 82 (0.0-268.8) months, 703 (13.6%) pts were diagnosed with distant mets, including 355 (6.9%) with CNS mets. Cumulative incidence of CNS mets was 0%, 2%, and 5% at 1, 2, and 5 years, respectively. Among pts with distant mets, the first site of distant mets was CNS only for 29 (4%), non-CNS only for 557 (79%), and both for 116 (17%) pts. At initial diagnosis of CNS mets, 195 (55%) pts were asymptomatic, and 46 (13%) had no active extracranial disease. Median time to any distant met was longer for pts who were diagnosed with CNS mets [40.0 (1.9-238.0) months] vs pts diagnosed with non-CNS mets only [31.4 (1.1-185.7) months, $p < 0.001$]. On multivariable analysis, risk of CNS mets was significantly associated with primary tumor location of scalp [Hazard Ratio (HR) 3.4, 95% Confidence interval (CI) 1.9-5.9], head/neck (HR 3.3, 95% CI 2.0-5.3), or trunk (HR 2.3, 95% CI 1.5-3.5) (vs upper extremity); acral lentiginous melanoma subtype (HR 2.0, 95% CI 1.2-3.6) (vs superficial spreading); increased T category (T2 HR 1.5, 95% CI 1.1-2.2; T3 HR 1.9, 95% CI 1.2-3.0; T4 HR 2.1, 95% CI 1.1-3.8; vs T1), Clark level (CL) (CL4 HR 2.1, 95% CI 1.2-3.7 vs CL2), and mitotic rate (MR) (MR 5-9/mm^2 HR 2.1, 95% CI 1.5-3.0; MR $> 9/mm^2$ HR 2.0, 95% CI 1.3-3.0; vs MR 0-4/mm^2). While high ($> 9/mm^2$) MR was associated with increased risk of CNS and non-CNS mets, intermediate (5-9/mm^2) was associated with CNS mets only. **Conclusions:** Primary tumor location, tumor thickness, and MR were strongly associated with risk of CNS mets. MR rate was more strongly associated with risk of CNS than non-CNS mets. Validation in independent cohorts may provide evidence to support CNS surveillance strategies in select pts with stage I-II CM who are deemed high risk for CNS mets. Research Sponsor: None.

9581 **Poster Session**

Genome-wide association study to reveal novel germline markers of melanoma survival.

Vylyny Chat, Robert Ferguson, Leah Morales, Una Moran, Min Jae Kim, Matija Snuderl, Iman Osman, Jeffrey S. Weber, Tomas Kirchhoff; New York University Medical Center, Manhattan, NY; New York University, New York, NY; The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY; NYU Grossman School of Medicine, New York, NY; Massachusetts General Hospital, Boston, MA; Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY; New York University School of Medicine, New York, NY

Background: Cutaneous melanoma (CM) is the most invasive form of skin cancer accounting for ~80% of all skin cancer related deaths. While tumor staging (based on recent AJCC classification) is routinely used in prognostic assessment, a large fraction of the outcomes is not explained by AJCC staging system. This urges for the discovery of a more personalized prognostic surrogates. Growing evidence highlights the role of germline genetics in CM progression; yet, to date no systematic prognostic germline study has been conducted in melanoma. We performed the first genome-wide association analysis (GWAS) to identify germline variants associated with melanoma survival. **Methods:** A cases/case GWAS was performed using the Infinium global screening array (GSA v3.0) to genotype 1,117 stage 0-III melanoma patients with no history of immunotherapy treatments ascertained at New York University Langone Health (NYULH). We randomly divided the study cohort into a discovery (N=630) and a validation (N=487) sets and tested the association of $>$ 5 million imputed germline variants with melanoma overall survival (OS) by fitting Cox-proportional hazard ratio (HR) regression in an additive genetic model adjusting for sex, age at diagnosis, AJCC 8th staging, tumor anatomic sites, and top 3 principal components. **Results:** We found 151 independent variants associated with melanoma OS ($p< 5\times10^{-5}$) in the discovery cohort. Two of these associations validated in the independent replication set (*Bonferroni* threshold for 151 tests: $p < 0.003$) with enhanced clinical and statistical significance in the pooled meta-analysis: rs4128212 [HR =2.47(1.75-3.48); $p=2.2\times 10^{-7}$], and rs13212644 [HR =2.59 (1.72-3.88); $p=4.2\times 10^{-6}$]. We further tested the combined effect of these two variants and found the presence of at least one risk allele of the variants associated with a substantially increased risk of death, surpassing GWAS level of significance (HR=3.74 (2.43-5.74); $p=1.5\times10^{-9}$). **Conclusions:** We present the results of first GWAS testing an association of germline variation with melanoma OS. Stemming from a unique patient population with extensive clinical follow-up data, we identified two prognostic germline loci with large HR effect size $>$2.5 that were independently validated. The observed association is independent of established histopathologic markers. While rs4128212 was mapped to a putative cancer prognostic gene locus (PLPP4: phospholipid phosphatase 4), rs13212644 was an eQTL (expression quantitative trait loci) for GCLC (Glutamate-Cysteine Ligase Catalytic Subunit), a key regulator in glutathione synthesis previously linked with favorable melanoma survival. The significantly enhanced combined effect of these two loci (HR $>$3.5; $p<5\times10^{-9}$) indicates a great promise for their clinical utility as independent personalized predictive markers of melanoma progression. Research Sponsor: U.S. National Institutes of Health.

9582 **Poster Session**

Granulomatous and sarcoid-like immune related adverse events (irAEs) in melanoma patients following CTLA4 blockade adjuvant therapy: An analysis of 1670 high-risk patients.

Arish Noor, Ibrahim Yassine, Sandra J. Lee, Megan Othus, James Moon, John M. Kirkwood, Vernon K. Sondak, Antoni Ribas, Kenneth F. Grossmann, Ahmad A. Tarhini; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of California, Los Angeles, Los Angeles, CA; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Fred Hutchinson Cancer Research Center, Seattle, WA; Fred Hutchinson Cancer Resaerch Center, Seattle, WA; University of Pittsburgh Medical Center, Pittsburgh, PA; Moffitt Cancer Center, Tampa, FL; University of California Los Angeles, Los Angeles, CA; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Granulomatous and sarcoid-like lesions (GSL) affecting the skin, lungs, thoracic lymph nodes, eyes and other organs following treatment with immune checkpoint inhibitors (ICIs) have been described in sporadic reports in the literature but the true incidence is unknown. **Methods:** We sought to estimate the incidence of GSL in the context of prospectively conducted ECOG-ACRIN E1609 phase III adjuvant trial in high-risk resected melanoma (N=1670 patients) testing ipilimumab 3 mg/kg (ipi3) and 10 mg/kg (ipi10) versus high-dose interferon-α (HDI). Descriptive statistics were used to calculate the incidence. **Results:** Among 1670 total patients treated with ICIs or with HDI in E1609, 1034 were treated with ipilimumab and 636 with HDI. Six GSL cases were reported among 1670 total patients treated with ipilimumab or with HDI as summarized in the table along with the corresponding CTCAE grades. More cases were observed with ipi10, followed by ipi3 and HDI, respectively. Organs involved included skin and subcutaneous tissue (granuloma annulare, granulomatous dermatitis), eye (ocular sarcoidosis), lymph nodes (noncaseating granulomatous lymphadenitis), lung and mediastinal lymph nodes (sarcoidosis, granulomatous inflammation). **Conclusions:** The incidence of granulomatous and sarcoid-like lesions (GSL) with adjuvant ipilimumab therapy in high-risk melanoma is rare. Reported cases ranged in grade from 1-3 and appeared manageable. Since most cases are asymptomatic, it is possible that GSLs are under-recognized and therefore, under-reported. A larger analysis including patients treated with anti-PD1 antibodies is currently underway. Clinical trial information: NCT01274338. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Organ(s)Involved	Ipi3 (N=523)	Ipi10 (N=511)	Total Ipi (N=1034)	HDI (N=636)
Ocular	-	1 (Gr 2)	1	-
Skin	-	1 (Gr 2)	1	-
Lung and Lymphatic	1 (Gr 3)	2 (Gr 3 x2)	3	1 (Gr 3)
Total (%)	1 (0.19%)	4 (0.78%)	5 (0.48%)	1 (0.16%)

9583 **Poster Session**

Adjuvant nivolumab in high-risk stage IIb/IIc melanoma patients: Results from investigator initiated clinical trial.

Melissa Wilson, Larisa J. Geskin, Richard D. Carvajal, Janice M. Mehnert, Cody Chiuzan, Benjamin Leiby, Katherine Senter, Lynn Mara Schuchter, Ryan Michael Weight, Michael J. Mastrangelo, Adam C. Berger; Sidney Kidney Cancer Center, Thomas Jefferson University, Philadelphia, PA; Columbia University Medical Center, New York, NY; Columbia University Irving Medical Center, New York, NY; NYU Grossman School of Medicine, New York, NY; Thomas Jefferson University, Department of Pharmacology and Experimental Therapeutics, Philadelphia, PA; Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Recent studies have shown 5-yr recurrence rates for Stage IIB and IIC melanoma of up to 46%. These high-risk patients currently have few options for adjuvant therapy to prevent this inevitable recurrence, with the only FDA approved therapy being high-dose interferon-alfa, which is quite toxic. However, there are now immunotherapies (anti-PD1) and targeted therapies (anti-BRAF and anti-MEK combinations) which are approved as adjuvants for Stage III patients, some of whom will have a lower baseline recurrence risk than those with Stage IIB/IIC melanoma. We sought to determine if adjuvant PD1 inhibition with nivolumab (N) would improve the recurrence free survival (RFS) compared to historical RFS rates. **Methods:** Our study (NCT03405155) is a single-arm, open label, multi-center, phase 2 clinical trial evaluating RFS at 24 months in patients with Stage IIB/IIC melanoma on treatment with N at 480 mg IV every 4 weeks for 12 cycles. Overall survival is a secondary endpoint. Associated translational research includes circulating tumor cell DNA and immune correlates. **Results:** Twenty three patients with Stage IIB and three patients with Stage IIC melanoma were enrolled onto the study and received at least one dose of N. At data cutoff, 22 patients remain in follow up, as four patients withdrew consent at different time points in the study – one patient after one dose who wished to discontinue, one due to concern for COVID and need for repeat visits, one due to insurance issues, and one due to recurrence and wish to discontinue (which was captured in study data and RFS calculations). Seventeen patients have been on the clinical trial for at least two years with nine patients having finished treatment but with less than two years follow-up; the median follow-up is currently 21.9 months. Two patients demonstrated melanoma recurrence, one after receiving cycle six of N and another one year after completing treatment, resulting in a 87.8% RFS (90% CI (64.2%-96.3%) at 2 years, compared to the historical RFS at 2 years of 70%. No N related serious adverse events (SAEs) were observed, with only 2% Grade 3 AEs observed (varied and unrelated to treatment) and all others were Grade 1-2, including 21% GI, 18% cutaneous, and 10% musculoskeletal, respiratory, and fatigue, each; overall, 2% of these Grade 1-2 AEs were treatment related. **Conclusions:** Our preliminary results show a trend towards improved RFS in patients with Stage IIB/IIC melanoma treated with nivolumab. The cohort has not reached a minimum follow up of at least 2 years for RFS; patients are continuing to be monitored. On study, we observed the expected adverse events, without evidence of new toxicities. Data maturation will reveal the full effect of adjuvant N on disease relapse and overall survival and distant metastasis-free survival in stage IIB/IIC melanoma patients. Clinical trial information: NCT03405155. Research Sponsor: BMS.

9584 **Poster Session**

Increased risk of immune-related hepatitis among adolescent and young adults (AYAs) with melanoma during immunotherapy with checkpoint inhibitors (ICIs).

Alicia Darwin, Damon R. Reed, Tawee Tanvetyanon; University of South Florida Morsani College of Medicine, Tampa, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Melanoma is the second most common malignancy affecting AYA patients after lymphoma. Nevertheless, AYA melanoma does constitute a minority of all melanoma cases. Additionally, the AYA population is not well represented in prospective clinical trials, including immunotherapy trials. While previous research has demonstrated the efficacy of ICIs across age groups, it remains unclear if toxicity profiles will be similar. In the general population, age-related changes in the immune milieu result in differential incidences of autoimmune diseases by age. This study aims to compare the toxicity profile between a cohort of AYA melanoma versus elderly melanoma patients receiving ICI therapy. **Methods:** In this single NCCN institutional study, electronic medical records of melanoma patients treated with ICIs between 01/2007-01/2019 were reviewed. Subjects receiving concurrent investigational agents or chemotherapy were excluded. The AYA cohort included those aged 15-40 years. The elderly cohort included those aged ≥65 years. Adverse events were coded according to CTC-AE version 5.0. Multivariable logistic regression analyses were performed. **Results:** Analyses included 184 treatment courses. In the AYA cohort (N = 57), median age at ICI initiation was 28.8 years (range: 17.9-39.3). In the Elderly cohort (N = 127), median age at ICI initiation was 72.3 years. More AYA patients (28.1% AYA vs. 7.9% Elderly) received ICI combination regimens. The most common adverse events amongst both cohorts were transaminitis (23.4%), rashes (49.5%), and diarrhea/colitis (20%). Incidences of pneumonitis, colitis, hypothyroidism, and hypophysitis did not differ significantly between cohorts. However, the AYA cohort experienced a higher incidence of transaminitis (38.6% AYA vs. 16.5% Elderly, $p = 0.001$) and increased occurrence of treatment related hospitalization (26.3% AYA vs. 7.1% Elderly, $p < 0.001$). Moreover, a higher proportion of severe grade ≥3 transaminitis occurred in the AYA group (27.3% AYA vs. 9.5% Elderly, $p = 0.004$). While occurrence of transaminitis was significantly associated with combination ICIs, the association between AYA status and transaminitis remained significant after adjusting for ICI regimen (OR 2.75, 95% CI: 1.3-5.8). There was a trend toward shorter time to transaminitis onset among the AYA than Elderly cohort (median 53.0 vs. 74.5 days [non-parametric $p = 0.28$]). To date, median survival has not been reached in both groups ($p = 0.09$). **Conclusions:** In this large cohort of AYA melanoma patients treated with ICI, we found a significantly higher incidence of immune-related transaminitis than in the Elderly cohort. Other immune-related AEs were comparable between cohorts. This finding was independent of ICI regimen. Further investigation will be needed to understand these differences between the AYA and Elderly cohorts. Research Sponsor: None.

TPS9585 **Poster Session**

S1801: A randomized trial of adjuvant versus neoadjuvant pembrolizumab for melanoma.

Sapna Pradyuman Patel, Megan Othus, James Moon, Michael Tetzlaff, Elizabeth Iannotti Buchbinder, Vernon K. Sondak, Michael C. Lowe, Catrina Mireles, Elad Sharon, Larissa A. Korde, Samantha Guild, William Edgar Carson, Antoni Ribas, Kenneth F. Grossmann; The University of Texas MD Anderson Cancer Center, Houston, TX; SWOG Statistical Center, Seattle, WA; UCSF Dermatopathology Service, San Francisco, CA; Beth Israel Deaconess Medical Center, Boston, MA; Moffitt Cancer Center, Tampa, FL; Department of Surgery, Emory University, Atlanta, GA; SWOG Operations Office, San Antonio, TX; National Cancer Institute, Bethesda, MD; Clinical Investigations Branch, National Cancer Institute, Bethesda, MD; AIM at Melanoma, San Rafael, CA; The Ohio State University Comprehensive Cancer Center, Columbus, OH; University of California Los Angeles, Los Angeles, CA; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: Although long term outcomes for most patients with early-stage melanoma is excellent following surgery, patients who have high-risk features such as lymph node involvement have poorer outcomes. Adjuvant therapy (AT) is currently considered for patients with stage III melanoma and selected patients with resected stage IV melanoma. Currently, AT for melanoma is anti-PD-1 or targeted therapy in the presence of a *BRAF* mutation. At this time, we are not able to predict which patients will derive benefit from AT and experience cure. While curative intent is the goal of treatment for primary melanoma, patients with bulky nodal involvement are at high risk of local or distant recurrence despite upfront surgery. Neoadjuvant treatment (NAT) offers the benefit of an early on-treatment pathological sample that can be profiled for biomarkers and correlated with response and survival. Treating with anti-PD1 while tumor remains visible in the body may generate a stronger immune response against *in vivo* tumor antigens compared to the traditional adjuvant setting where antigen is presented by microscopic residual tumor burden. Pilot studies of NAT with anti-PD-1 therapy have been initiated in melanoma. Multidisciplinary coordination in these cases is paramount. In these studies, an improvement in relapse-free survival and overall survival has been observed; additionally, pathologic response rates to NAT have been estimated in small studies. **Methods:** S1801 is a randomized phase II study of AT versus NAT with pembrolizumab (PEM, NCT03698019). Patients with measurable, clinically detectable and resectable cutaneous, acral, and mucosal melanomas without brain metastasis are eligible. Patients with Stage IIIB to oligometastatic, resectable Stage IV are randomized 1:1 to AT or NAT. Patients getting AT undergo surgery first followed by 18 doses of PEM 200 mg IV every 3 weeks. Patients getting NAT receive 3 doses of pre-operative PEM followed by surgery and then 15 doses of adjuvant PEM. Radiation may be given on either arm after surgery, at the investigator's discretion. Primary endpoint is event-free survival measured from the date of randomization to the date of first documented progression that renders the patient unable to receive planned protocol surgery, failure to begin adjuvant therapy within 84 days of surgery, relapse after surgery, or death due to any cause. Secondary endpoints include RECIST and iRECIST response rates, as well as a number of surgical outcomes. Safety monitoring is conducted with disease progression and toxicity thresholds. The key Translational Medicine objective of this trial is to determine the pathologic response rate to NAT after 3 doses of PEM. Surgical pathology grossing instructions to ensure readout for pathologic response are provided in the form of training slides. Enrollment is at 40% of a planned 500 patients. Clinical trial information: NCT03698019. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS9586 **Poster Session**

Combination of radiomic and biomarker signatures as exploratory objective in a phase II trial with intratumoral BO-112 plus pembrolizumab for advanced melanoma.

Ivan Marquez-Rodas, Stéphane Dalle, Eduardo Castanon, Miguel F. Sanmamed, Ana Maria Arance, Pablo Cerezuela-Fuentes, Roberto Martin Huertas, Juan Francisco Rodríguez-Moreno, Maria Gonzalez-Cao, Eva Muñoz-Couselo, Juan Martin-Liberal, Delvys Rodriguez-Abreu, Ángel Alberich-Bayarri, Irene Mayorga-Ruiz, Miguel Angel Molina Vila, Ruth Román, Marya F. Chaney, Javier Sánchez López, Sonia Maciá, Marisol Quintero; Medical Oncology, General University Hospital Gregorio Marañón & CIBER-ONC, Madrid, Spain; Hospices Civils de Lyon, Pierre Bénite, France; Clínica Universidad de Navarra, Madrid, Spain; Department of Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain; Department of Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Medical Oncology. Hospital Virgen de la Arrixaca, Murcia, Spain; Hospital Clínic Barcelona, Barcelona, Spain; Hospital Universitario Sanchinarro-Clara Campal, Madrid, Spain; Instituto Oncológico Dr Rosell, Quirón Dexeus University Hospital, Barcelona, Spain; Vall d'Hebron Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Institut Català d'Oncologia, Barcelona, Spain; Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas De Gran Canaria, Spain; Quibim, Valencia, Spain; Pangaea Oncology, Barcelona, Spain; Merck & Co., Inc., Kenilworth, NJ; Highlight Therapeutics, Valencia, Spain

Background: Intratumoral immunotherapies are gaining interest in oncology, particularly in melanoma. These therapies, however, have faced some issues. For instance, standard response criteria do not accurately describe tumor burden, and responses may differ for injected/non injected lesions. Besides, target lesions may become non evaluable. Biomarkers provide interesting information for these therapies. In addition, some radiomic signatures have been associated with CD-8 infiltration. BO-112 is a double stranded synthetic RNA formulated with polyethyleneimine (PEI) that mimics a viral infection, mobilizing the immune system and changing tumor microenvironment. Clinical data are available from a first-in-human study, which showed ORR of 11% and DCR of 46% in patients who had developed progressive disease on immunotherapy. In patients with melanoma, this ORR was 20%. A phase 2 clinical study of BO-112 with pembrolizumab in patients with liver metastases from digestive tumors is ongoing. Both studies brought up data regarding how some biomarkers are increased after a single dose of BO-112 and correlated with responses. In this phase II study in patients with pretreated melanoma (NCT04570332), we will prospectively assess CD-8 and PD-L1 by immunohistochemistry, which will be compared with multi-parametric radiologic findings and correlated with clinical benefit. In addition, retrospective DNA sequencing will be performed. This kind of exploratory analysis in intratumoral immunotherapies might be key to identify predictive and prognostic factors. **Methods:** Phase 2, single arm, open label study of BO-112 with pembrolizumab in patients with advanced melanoma. BO-112 is administered once weekly (QW) in 1 to 8 tumor lesions, total dose 1-2 mg (depending on the number of injected lesions), for the first 7 weeks and then once every three weeks (Q3W); pembrolizumab 200 mg will be administered Q3W. Key eligibility criteria: advanced cutaneous or mucosal melanoma; patients must have progressed on or after treatment with an antiPD-1/L1 mAb; at least one measurable lesion amenable for weekly IT injection. Primary efficacy variable is ORR by RECIST 1.1, assessed by independent central radiologist (QUIBIM Precision platform). A 1-sided alpha of 4.19% and power of 81.8% are used. If less than 8 patients out of 40 have ORR, the study will not meet the statistical bar. Secondary endpoints include clinical activity by RECIST1.1 and iRECIST, overall survival, safety and PKs. Exploratory objectives include itRECIST and evaluation of CD-8 and PD-L1 expression by immunohistochemistry (Pangaea laboratory), which will be correlated with radiomic signatures (first order and second order) from standard-of-care computed tomography (CT) images. Enrollment is open and 1 of planned 40 patients has been enrolled. Nineteen sites are planned to participate. Clinical trial information: NCT04570332. Research Sponsor: Highlight Therapeutics, SL.

TPS9587 **Poster Session**

CAcTUS: A parallel arm, biomarker driven, phase II feasibility trial to determine the role of circulating tumor DNA in guiding a switch between targeted therapy and immune therapy in patients with advanced cutaneous melanoma.

Rebecca Lee, Dominic G. Rothwell, Shien Chow, Heather May Shaw, Samra Turajlic, Nigel Smith, Alexandra Clipson, Harry Clarke, Noel Kelso, Jackie Mitchell, Chris Sutton, Gema Sylvestre, Paul D. Nathan, James Larkin, Philippa Gail Corrie, Elizabeth Ruth Plummer, Richard Marais, Caroline Dive, Paul Lorigan; The Christie NHS Foundation Trust, Manchester, United Kingdom; Cancer Research UK Manchester Institute Cancer Biomarker Centre, Manchester, United Kingdom; The Clatterbridge Cancer Centre, Wirral, United Kingdom; Mount Vernon Cancer Centre, Bucks, United Kingdom; The Institute of Cancer Research, London, United Kingdom; Molecular Oncology group, Cancer Research UK Manchester Institute, Manchester, United Kingdom; The University of Manchester, Manchester, United Kingdom; Mount Vernon Cancer Centre, Northwood, United Kingdom; Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Newcastle University and Northern Centre for Cancer Care, Newcastle Hospitals NHS Trust, Newcastle upon Tyne, United Kingdom; Molecular Oncology Group, Cancer Research UK Manchester Institute, Manchester, United Kingdom; University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom

Background: Circulating tumor DNA (ctDNA; the tumour derived fraction of circulating free DNA in the blood) has been shown to be a biomarker of tumor burden/progression in many cancers. We recently accurately monitored treatment response and resistance in stage IV melanoma by ctDNA analysis in serial peripheral blood samples. Pre-clinical data has previously revealed that BRAF inhibition provokes a micro-environment with increased T cell infiltration, improved T cell recognition of melanoma associated antigens and reduced production of immunosuppressive cytokines that could enhance immune responses. We aimed to test the hypothesis that ctDNA could be implemented as a personalised, real-time liquid biopsy to identify when tumours are responding to targeted therapy in order optimise a switch to immunotherapy. **Methods:** We validated the ctDNA assays for BRAF mutation calling as a primary trial endpoint. We designed a phase II multicenter, parallel arm study across 6 UK sites, to assess primary objectives of i). Whether a ctDNA result can be turned around within 7 days and actioned in a clinically relevant timeframe ii). to assess whether a decrease in ctDNA levels of mutant *BRAF* by $\geq$80% from baseline on targeted therapy is an appropriate 'cut off' to instruct switching to immunotherapy. Secondary endpoints include Overall Response Rate (ORR) to immunotherapy, radiological/clinical and ctDNA determined progression free survival (PFS) on each treatment. Forty patients are planned based on inclusion criteria of stage IV or stage III unresectable cutaneous *BRAF* mutant melanoma, baseline ctDNA *BRAF* variant allele frequency (VAF) $\geq$1.5%, ECOG 0/1/2, no symptomatic brain metastases, no prior adjuvant nivolumab plus ipilimumab (N+I). Prior adjuvant dabrafinib + trametinib (D+T) is allowed as long as recurrence is $>$6 months from completion. Patients are randomised 1:1 to either standard Arm A; investigator choice of either D+T (150mg BD +2mg OD respectively) or N+I (1 mg/kg N +3 mg/kg I q3 wkly, then N 480mg q4 wkly) first line, then switch on progression to the other treatment. In the experimental Arm B; all patients start on D+T and have *BRAF* ctDNA monitored q2 wkly for 4 wks then q4 wkly. When $\geq$80% decrease vs. baseline in ctDNA *BRAF* VAF occurs, patients switch to N+I. If patients subsequently progress on N+I, they will resume D+T. The study is open with 9 patients enrolled at time of submission. Clinical trial information: NCT03808441. Research Sponsor: Bristol Myers Squibb, The Christie Charity and Cancer Research UK.

TPS9588 **Poster Session**

Clinical trial in progress: Phase II trial of defactinib (VS-6063) combined with VS-6766 (CH5126766) in patients with metastatic uveal melanoma.

Rino S. Seedor, Marlana Orloff, J. Silvio Gutkind, Andrew E. Aplin, Mizue Terai, Erin Sharpe-Mills, Haley Klose, Michael J. Mastrangelo, Takami Sato; Fox Chase Cancer Center, Philadelphia, PA; Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; UCSD, San Diego, CA

Background: Despite successful treatment of primary uveal melanomas (UM), up to 50% of patients subsequently develop systemic metastasis, with the liver involved in up to 90% of patients. Currently there is no US FDA-approved treatment for metastatic uveal melanoma (MUM). Activating mutations in genes encoding alpha subunits of the heterotrimeric G proteins, GNAQ and GNA11, are found in 80-90% of UM. Recent information suggests that *GNAQ/GNA11*-oncogenic signaling involves a non-canonical pathway conferring the activation of YAP1, distinct from the activation of PLCβ and PKC-MEK-ERK, which may explain the failure of MEK inhibitors in MUM patients. Focal Adhesion Kinase (FAK) is a tyrosine kinase that provides a direct link between Gαq and tyrosine phosphorylation networks controlling YAP and UM growth. Interestingly, UM represents the human cancer harboring the highest level of FAK overexpression. Recent kinome-wide CRISPR-Cas9 screens revealed that FAK and RAF/MEK co-targeting may provide a new network-based precision therapeutic strategy for MUM treatment. **Methods:** This is an investigator-initiated, prospective, single arm, single-institution, phase II trial evaluating the combination of a FAK inhibitor (defactinib, VS-6063) with a RAF/MEK inhibitor (VS-6766, CH5126766) for the treatment of patients with metastatic uveal melanoma [NCT04720417]. The primary endpoint of the study is disease control rate (DCR) of 50% including complete response (CR), partial response (PR), and stable disease (SD) as determined by RECIST criteria version 1.1. Secondary endpoints include progression free survival, overall survival, and causality of adverse events. Exploratory endpoints include analysis of the pharmacodynamic profile, mechanism of resistance to the combination, and investigation of circulating free DNA as a biomarker. The efficacy of this combination treatment will be assessed using the Simon's two stage design. In stage I, a total number of 8 patients are accrued and if there are 2 or fewer overall responses among these 8 patients, further enrollment of patients may be stopped with the conclusion that DCR cannot be 50% or greater. Otherwise, an additional 10 patients will be accrued in stage II, resulting in a total sample size of 18 patients. Patients at 18 years or older with metastases from uveal melanoma will be eligible (any line of therapy). Defactinib (200 mg) will be administered orally twice a day in combination with VS-6766 (3.2 mg) administered orally twice a week for 3 weeks, in 28-day cycles. Dose modification will be considered based on toxicity. Treatment will be continued until maximum clinical benefit is obtained; disease progression or the development of intolerable side effects. Enrollment to stage 1 began in February 2021. Clinical trial information: NCT04720417. Research Sponsor: Verastem Oncology, Inc.

TPS9589 **Poster Session**

Ipilimumab, nivolumab and tocilizumab as first-line therapy for advanced melanoma.

Inderjit Mehmi, Omid Hamid, F. Stephen Hodi, Melinda Vassalo, Saundra Malatyali, Swathi Krishnarajapet, Nan O'Donnell, Angeli Castrence, Eunice Lim, Jill Gormley, Jeffrey S. Weber; The Angeles Clinic & Research Institute, A Cedar-Sinai Affiliate, Los Angeles, CA; The Angeles Clinic and Research Institute, Los Angeles, CA; Dana-Farber Cancer Institute, Boston, MA; The Laura and Issac Perlmutter Cancer Center, NYU Langone Health, New York, NY; Perlmutter Cancer Center at NYU Langone, New York, NY; Perlmutter Cancer Center and NYU Langone, New York, NY; The Angeles Clinic and Research Institute, Inc., Los Angeles, CA; The Angeles Clinic and Research Institute, An Affiliate of Cedar-Sinai, Los Angeles, CA; Dana Farber Cancer Institute, Boston, MA; Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: Interleukin 6 (IL-6) functions in the maintenance of hepatocytes, haemotopoietic progenitor cells, a variety of other tissues, and regulates the innate and adaptive immune system. IL-6 may play a role as a chronic inflammatory mediator in altering levels of acute phase proteins synthesized by the liver and circulating myeloid cells which have been shown to be associated with short survival with checkpoint inhibition and which are immune suppressive. The immunomodulatory properties of interleukin-6 may in part also be responsible for immune related adverse events, given the reversal of those toxicities observed with IL-6 receptor blockade in clinical practice. To assess if blockade of IL-6 binding is associated with a decrease in irAEs and/or an increase in efficacy defined as overall response rate (ORR) at week 24 in patients receiving ICB, we added tocilizumab to ipilimumab and nivolumab therapy. **Methods:** The current phase II trial is a two-stage design to assess the safety, tolerability, and grades 3-5 immune related toxicities of tocilizumab administered every 6 weeks up to week 24 in combination with ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg every 3 weeks for 4 doses each during a 12 week induction period, then administered every 6 weeks with nivolumab at 240 mg flat dose every 2 weeks in maintenance for up to 24 weeks, and nivolumab alone will be given at 480 mg flat dose every 4 weeks thereafter for up to 2 years. Eligible patients include those age 18 or older with measurable and unresectable stages III/IV melanoma (cutaneous, acral, mucosal), without prior systemic treatment for metastatic disease. Adjuvant therapy (IFN-alpha, ipilimumab and/or nivolumab, or pembrolizumab) is allowed. Patients with metastatic melanoma of brain are allowed, if neurologically stable and off immunosuppressive steroids. A total of 18 patients will be treated in the first stage, and 49 additional patients in the second stage for a total of 67. The comparator data are from the N3I1 arm of Checkmate-511 trial, in which treatment-related grades 3-5 irAEs were 33.9% with a 45.6% response rate (1). Prespecified activity goal for the first stage of accrual has been met; second stage accrual began in January 2021. References: (1) Lebbé C, Meyer N, Mortier L, Marquez-Rodas I, et al. Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. Journal of Clinical Oncology 2019 37:11, 867-875. Clinical trial information: NCT03999749. Research Sponsor: BMS and Genetech.

TPS9590 **Poster Session**

NCT04552223: A phase II study of nivolumab plus BMS-986016 (relatlimab) in patients with metastatic uveal melanoma (UM) (CA224-094).

Jose Lutzky, Lynn G. Feun, Norma Magallanes, Deukwoo Kwon, J. William Harbour; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; Sylvester Comprehensive Cancer Center, Miami, FL; Bascom Palmer Eye Institute, Miami, FL

Background: Uveal melanoma (UM) is a rare disease but 50% of patients will eventually develop metastatic disease, for which not effective therapy is available. Liver-directed therapies, immunotherapy, targeted therapy and chemotherapy have limited activity [1]. Lymphocyte activation gene 3(LAG-3) is an immune checkpoint receptor associated with decreased T-cell effector function and tumor escape. Preclinical models have shown that dual inhibition of LAG-3 and PD-1 blockade generates synergistic anti-tumor activity [2]. Recent preclinical data indicates that uveal melanoma CD8+ T cells express the checkpoint receptor LAG3 to a greater extent than PD1 or CTLA4 [3,4]. Therefore, LAG3 is a potential candidate for checkpoint inhibitor immunotherapy in UM. Relatlimab is a human LAG-3-specific antibody isolated from immunized transgenic mice which binds to a defined epitope on LAG-3 with high affinity and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC Class II. **Methods:** This is an open-label, single arm, single site investigator-initiated phase II study, NCT04552223. Based on Simon two-stage minimax design, 13 patients will be enrolled in Stage 1. If at least one response is noted, the study will proceed to Stage 2 and enroll an additional 14 patients. The null hypothesis will be rejected if 4 or more responses are observed among 27 patients. This design achieves 5% type I error and 80% power when the true ORR is 20%. The trial opened to accrual in December 2020. As of February 15, 2021 four patients had been enrolled the first stage of accrual. Main eligibility criteria include patients with biopsy proven metastatic uveal melanoma, previously untreated with PD-1, CTLA-4 and/or LAG-3 blocking antibodies and in good performance status. Enrolled patients are treated in the outpatient setting. Nivolumab 480 mg is mixed in the same bag with relatlimab 160 mg and administered intravenously over 60 minutes every 4 weeks until disease progression or intolerable toxicity for up to 24 months. The primary endpoint is best objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS), overall survival (OS), median duration of response (mDOR), and adverse events (AEs). Correlative studies will evaluate pre- and post-treatment characteristics of T cells in the tumor microenvironment and blood. Clinical trial information: NCT04552223. Research Sponsor: Bristol Myers Squibb, Sylvester Cancer Center trials grant.

TPS9591 **Poster Session**

Phase I/II trial of intratumoral administration of hu14.18-IL2, with local radiation, nivolumab, and ipilimumab in subjects with advanced melanoma.

Mark R. Albertini, Zachary Scott Morris, Jacquelyn A Hank, Erik Ranheim, Cindy L Zuleger, Kimberly McDowell, Renae M Quale, Molly Monson, Erin Clements, Tamara Koehn, Heather B. Neuman, Sharon M. Weber, Jennifer Racz, Mary Beth Henry, Emily Reinstad, KyungMann Kim, Stephen D. Gillies, Paul M. Sondel; University of Wisconsin, Madison, WI; University of Wisconsin, School of Medicine and Public Health, Madison, WI; University of Wisconsin Carbone Cancer Center, Madison, WI; UW Carbone Cancer Center, Madison, WI; University of Wisconsin School of Medicine and Public Health, Madison, WI; University of Wisconsin Department of Surgery, Madison, WI; Provenance Biopharmaceuticals Corporation, Carlisle, ME; University of Wisconsin-Madison, Madison, WI

Background: We are studying an intratumoral (IT) in situ vaccine strategy using the GD2-reactive hu14.18-IL2 immunocytokine (hu-IC) to convert the injected tumor into a site of enhanced tumor antigen presentation, as has been shown in mice. Hu-IC is a humanized monoclonal antibody (mAb) covalently linked to two molecules of IL-2 at the Fc region. The hu14.18 mAb recognizes GD2, a disialoganglioside found in tumors of neuroectodermal origin. We previously studied intravenous (IV) hu-IC and reported immune activation and reversible toxicities (1). Surgery to resect recurrent stage III or stage IV melanoma combined with 3 courses of IV hu-IC resulted in prolonged tumor-free survival in some patients (2). Murine GD2+ tumor models showed enhanced antitumor activity and recruitment of T cells using hu-IC IT versus IV (3). In these models, the combination of radiation therapy (RT) followed by IT hu-IC dramatically potentiates the antitumor response and enhanced response to immune checkpoint blockade (4). Biological samples (blood and tumor) will be interrogated to identify biological mechanisms and develop biomarkers for future testing. **Methods:** This outpatient phase I/II trial uses a 3 + 3 design to determine maximum tolerated or maximum administered dose of IT hu-IC (planned dose level: 2 mg/m^2/day; de-escalation dose level: 1 mg/m^2/day) when given alone (Phase 1A: 3-12 patients), after RT (Phase 1B: 6-12 patients), after RT and in combination with nivolumab (Phase 1C: 6-12 patients), and after RT and in combination with nivolumab and ipilimumab (Phase 1D: 31-34 patients). The trial will evaluate safety, antitumor activity, and immunologic endpoints and includes an expanded Phase II cohort (Phase 1D). The IT injections (once daily x 3 days) are delivered every 21 days for 4 cycles and can then continue every 28 days for up to 13 cycles if there is response/stable disease and residual injectable tumor. Key inclusion criteria: 1) histologically proven, malignant melanoma that is advanced (Stage IV) or surgically incurable; 2) at least 1 (preferably 2) sites of disease amenable to safe repeated IT injections; and 3) must have received or declined at least one FDA approved therapy, either in the adjuvant setting or for metastatic disease, with an impact on survival. Two subjects have been accrued into Phase IA as of 2-4-2021. References: (1)King DM, et al. J Clin Oncol 22:4463-4473, 2004. (2)Albertini MR, et al. Can Imm Imm 67(10):1647-1658, 2018. (3)Yang RK, et al. J of Imm 189:2656-2664, 2012. (4)Morris ZS et al. Can Res 76:3929-3941, 2016. Clinical trial information: NCT03958383. Research Sponsor: U.S. National Institutes of Health, Other Foundation, U.S. National Institutes of Health, Philanthropic gifts to the UWCCC.

TPS9592 **Poster Session**

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.

Alexander Christopher Jonathan Van Akkooi, Paolo Antonio Ascierto, Paul D. Nathan, Paul Nghiem, Philip Reimann, Frank Hermann, Jürgen C. Becker; Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; Mount Vernon Cancer Centre, Northwood, United Kingdom; University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; 4SC AG, Planegg-Martinsried, Germany; Translational Skin Cancer Research, Deutsches Konsortium für Translationale Krebsforschung (DKTK), Essen, Germany

Background: Merkel cell carcinoma (MCC) is a rare but highly aggressive human skin cancer often caused by the Merkel cell polyomavirus or extended exposure to sunlight. Since the approvals of avelumab globally and subsequently pembrolizumab (US only), anti–PD–(L)1 antibody therapies have become the standard of care for advanced/metastatic MCC patients in recent years. Still, a significant proportion of MCC patients do not respond to or relapse on anti–PD–(L)1 antibody monotherapy. Recent preclinical data suggest that the small molecule, selective class I histone deacetylase inhibitor (HDACi) domatinostat can 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 allowing a reintroduction of anti–PD–(L)1 therapy for an improved and sustained clinical benefit. **Methods:** The study is a phase II, multicenter, single arm clinical trial of the orally administered HDACi domatinostat in combination with the anti–PD–(L)1 antibody avelumab for patients with advanced unresectable/metastatic MCC that are progressing on previous anti–PD–(L)1 therapy. ClinicalTrials.gov Identifier: NCT04393753. Key Inclusion Criteria are: histologically confirmed MCC, an ECOG performance status $\leq$ 1, MCC in an advanced, unresectable stage III or metastatic stage IV, and progressing on previous anti–PD–(L)1 antibody monotherapy within the last 12 weeks before planned first administration of study medication. Key Exclusion Criteria are: history of serious anti–PD–(L)1 therapy related adverse reactions prohibiting further avelumab treatment, more than one line of previous systemic anti neoplastic therapy other than anti–PD–(L)1 antibody monotherapy (excluded: palliative radiation therapy of single lesions within 2 weeks before planned administration of study medication), significant active or chronic disease (infections, immunodeficiencies, cardiovascular, psychiatric disorders). A total of 40 patients will be enrolled in up to 46 clinical study sites in Europe and USA. Anti-tumor activity will be primarily assessed by the objective response rate according to RECIST v1.1 as an exploratory analysis. Secondary objectives include additional efficacy assessments, safety, quality of life and pharmacokinetics of domatinostat in combination with avelumab. Correlative aims include evaluating biomarkers for association with clinical benefit. The first patient was enrolled on Oct. 16, 2020, 21 of 46 clinical sites are active and 4 out of 40 planned patients have been enrolled as of Feb. 15, 2021. Clinical trial information: NCT04393753. Research Sponsor: 4SC AG.

TPS9593 **Poster Session**

Winship 4851-19: A pilot study of neoadjuvant and adjuvant cemiplimab for high-risk cutaneous squamous cell carcinoma.

Michael C. Lowe, Melinda Lynne Yushak, Keith A. Delman, Monica Rizzo, Caroline Claar, Allyson Schmidt, Jeffrey M. Switchenko, David H. Lawson, Ragini Reiney Kudchadkar; Department of Surgery, Emory University, Atlanta, GA; Emory University School of Medicine, Atlanta, GA; Emory Univ, Atlanta, GA; Emory University, Atlanta, GA; Emory University, Department of Biostatistics and Bioinformatics, Atlanta, GA; Winship Cancer Institute of Emory University, Atlanta, GA; Winship Cancer Institute, Atlanta, GA

Background: The PD-1 inhibitor cemiplimab was approved in 2018 for treatment of locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable with surgery or radiation. This approval was based on the results of the phase 2 EMPOWER-CSCC-1 trial, which demonstrated an objective response rate of 47% with a significant number of these patients experiencing a durable response. However, patients with high risk cSCC that are able to undergo curative intent surgery are not candidates for checkpoint inhibitor therapy but still experience high rates of recurrence and/or systemic progression even when offered adjuvant radiotherapy. In light of data using checkpoint inhibitor therapy in the neoadjuvant setting in other cutaneous malignancies, we hypothesized that cemiplimab therapy would improve surgical outcomes and reduce long-term recurrence rates in patients with high-risk resectable cSCC if used in the perioperative setting. **Methods:** Winship 4851-19 is a single arm pilot study of cemiplimab in the neoadjuvant and adjuvant setting for high-risk resectable cSCC (NCT04428671). In the neoadjuvant phase, patients receive three doses of cemiplimab every three weeks followed by standard of care surgery. Radiation may be offered when clinically appropriate at the discretion of the investigator. In the adjuvant phase (following surgery +/- radiation), patients receive cemiplimab every three weeks to complete one year total of treatment. Eligible patients must have surgically resectable histologically proven high risk cSCC defined as: nodal disease with extracapsular extension or one node $\geq$20mm; in transit metastases $>$ 2cm from primary lesion; T4 head and neck primary tumor; perineural invasion; or recurrent cSCC with concurrent $\geq$N2b nodal disease, size $\geq$4cm or bony invasion, or poorly differentiated histology. Patients cannot have received prior immunotherapy and must have a ECOG performance status of 0 or 1. Primary objective is to establish pathologic response rate. Secondary objectives include assessments of local and distant recurrence and overall survival rates. We also plan to evaluate the immune profile of fresh tumor and blood to assess the impact of neoadjuvant cemiplimab on the tumor microenvironment and circulating immune responses. To date 5 of 20 patients have been enrolled; this sample size was selected based on feasibility and ability enroll within a timely fashion. Clinical trial information: NCT04428671. Research Sponsor: Regeron.

TPS9594 **Poster Session**

Phase II study of binimetinib with imatinib in patients with unresectable KIT-mutant melanoma.

Katy K. Tsai, Iwei Yeh, Adil Daud, Ari Oglesby; University of California, San Francisco, San Francisco, CA

Background: Immune checkpoint inhibitors (ICI) have transformed treatment for patients (pts) with advanced melanoma, as have BRAF/MEK inhibitors for pts with BRAF V600-mutant melanoma. However, pts with acral or mucosal melanomas are in particular need of more options given a lower objective response rate (ORR) to ICI, and lower incidence of BRAF V600 driver mutation. Such BRAF mutations are found in only 5-10% of acral/mucosal melanomas, while KIT mutations/amplifications are found in 10-20%. Even when present, a KIT alteration does not guarantee response to KIT inhibition, with only about one-third responding as previously shown in 3 phase II studies. A significant number of KIT-mutant melanomas have been shown to demonstrate NF1 or SPRED1 loss, with recent preclinical work showing that such alterations are associated with the loss of negative suppression of RAS, resulting in RAS activation and MEK dependence. We hypothesize that NF1 or SPRED1 loss cooperates with KIT mutations to drive melanomagenesis and resistance to KIT inhibition, and propose to target this vulnerability with a combination approach to targeted therapy. This phase II study will be the first to evaluate the efficacy and safety of binimetinib plus imatinib in pts with KIT-mutant melanoma. **Methods:** This is an investigator-initiated phase II study of binimetinib in combination with imatinib in pts with BRAF V600 WT, KIT-mutant unresectable melanoma who have progressed on or who are ineligible for ICI (NCT04598009). Pts will be $\geq$18 yo with performance status ECOG 0-2, and have unresectable Stage IIIB/C/D or Stage IV melanoma that is BRAF V600 WT and KIT-mutant by CLIA-certified testing platform. Pts will have progressed on prior ICI or other standard-of-care (SOC) therapies, or be ineligible for or unable to tolerate SOC therapies. Pts with brain metastasis will be eligible if clinically stable and determination made that no CNS-specific treatment is required prior to study start. Pts previously treated with a MEK inhibitor will be excluded. A Simon 2-stage Minimax design will be used; the null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. 15 pts will be accrued in the first stage. If there are £1 responses, the study will be stopped. Otherwise, 10 additional pts will be accrued for a total of 25. The null hypothesis that the true response rate is 0.1 will be rejected if $\geq$6 responses are observed. This yields a type I error rate of 0.05 and power of 0.8017 when the true response rate is 0.3.Primary endpoint: ORR (RECIST). Secondary endpoints: duration of response, progression-free survival, overall survival, clinical benefit rate (CR, PR, or SD $\geq$16 weeks), safety profile (CTCAE). Exploratory objectives to include investigations of association between clinical response and baseline NF1 and SPRED1 status, and of pathologic correlates of acquired resistance. Study began enrolling pts in December 2020 and is ongoing. Clinical trial information: NCT04598009. Research Sponsor: Array/Pfizer.

TPS9595 **Poster Session**

Phase Ib/randomized phase II study combining hepatic percutaneous perfusion with ipilimumab plus nivolumab in advanced uveal melanoma: The CHOPIN trial.

Thaïs M.L. Tong, Mark C. Burgmans, Monique Van der Kooij, Frank M. Speetjens, Arian R. van Erkel, Rutger W. van der Meer, Shelley van den Bosch, Mare A. Jonker, Inge C.F.M. Roozen, Jacob Lutjeboer, Fenna Rijksen, Els L. van Persijn-van Meerten, Chris H. Martini, Remco W.M. Zoethout, Fred G.J. Tijl, Christian U. Blank, Ellen Kapiteijn; Leiden University Medical Center, Department of Medical Oncology/Radiology, Leiden, Netherlands; Leiden University Medical Center, Department of Radiology, Leiden, Netherlands; Leiden University Medical Center, Department of Medical Oncology, Leiden, Netherlands; Leiden University Medical Center, Department of Anesthesiology, Leiden, Netherlands; Leiden University Medical Center, Department of Extra Corporal Circulation, Leiden, Netherlands; Netherlands Cancer Institute (NKI-AVL), Department of Medical Oncology, Amsterdam, Netherlands

Background: Uveal Melanoma (UM), although rare, is the most common intraocular malignant tumor in adults. Despite successful treatment of the primary tumor, approximately half of all patients will develop metastatic disease, mainly in the liver. Prognosis of metastatic UM is poor and overall survival (OS) has not improved over the last 30 years. Effective systemic therapies are lacking but recent literature suggests an improved effect of the combination of immunotherapy with ipilimumab/nivolumab (IPI/NIVO) as opposed to monotherapy. Percutaneous hepatic perfusion (PHP) is a liver-directed therapy that allows delivery of a high dose of melphalan to the liver with limited systemic toxicity. Efficacy of PHP has been demonstrated in phase II trials including patients with liver-dominant or liver-only metastases. In this study we combine PHP with IPI/NIVO with the goal of inducing a synergistic effect and improving disease control. The aim of the phase 1b is to establish the maximum tolerated dose (MTD) of IPI/NIVO when combined with PHP. The following randomized phase II trial aims to determine the efficacy of IPI/NIVO combined with PHP, compared to PHP alone. **Methods:** We initiated a prospective, single center, phase Ib and randomized phase II trial with a maximum of 88 patients in total. Patients with confirmed measurable hepatic UM metastases according to RECIST 1.1 and WHO performance score of 0-1 are included. Exclusion criteria are age $>$ 75 years, treatment with systemic immunosuppressive medication and prior systemic treatment for metastasic UM. Phase Ib is a dose-escalation study consisting of two cohorts. The dose of IPI and NIVO is increased from 1mg/kg and 1mg/kg in cohort 1, to 1mg/kg and 3mg/kg, in cohort 2, respectively. The melphalan dose for the PHP is 3mg/kg (maximum dose of 220mg) in both cohorts. Treatment duration is 12 weeks consisting of 4 courses of IPI/NIVO with 2 PHP's in week 1 and 7. In phase II, the same treatment scheme as phase Ib is used in the treatment arm combining IPI/NIVO with PHP at the established MTD. The second treatment arm consists of 2 PHP's performed at a 6 week interval. Follow-up includes laboratory tests, CT-chest/abdomen and MRI-liver. Safety and toxicity are assessed according to the CTCAE V5.0. Radiological response is assessed according to RECIST 1.1 and irRECIST. Primary objective of phase Ib is to determine safety of the combination of IPI/NIVO with PHP defined by the MTD. In phase II the primary objective is the efficacy of combination treatment of IPI/NIVO with PHP defined by progression-free survival at one year. Secondary objectives include OS and overall response rate. Cohort 1 and 2 of phase Ib have been completed without dose limiting toxicities and the MTD is defined as IPI 1 mg/kg and NIVO 3 mg/kg. Accrual to phase II started in December 2020. An update will be presented at ASCO 2021. Clinical trial information: NCT04283890. Research Sponsor: Bristol Myers-Squibb and Delcath System Inc.

TPS9596 **Poster Session**

Multicenter phase I/II trial of encorafenib with and without binimetinib in combination with nivolumab and low-dose ipilimumab in metastatic BRAF-mutant melanoma.

Max Jameson-Lee, Patrick Alexander Ott, Jason J. Luke, Michael A. Postow, Andrew Stewart Poklepovic; UPMC Hillman Cancer Center, Pittsburgh, PA; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; VCU Massey Cancer Center, Richmond, VA

Background: Targeted therapy (BRAF + MEK inhibitors) and immunotherapy (anti-PD1 + anti-CTLA4) have improved overall survival for metastatic or unresectable *BRAF*$^{V600E/K}$mutant melanoma. Whereas targeted therapy has a high response rate, immunotherapy may deliver longer term disease control for a larger number of patients. Despite these treatments, patients with high risk metastatic melanoma such as those with brain or liver metastases, elevated lactate dehydrogenase (LDH) and bulky disease have inferior treatment outcomes with current therapies. A BRAF+MEK+PDL1 regimen has recently emerged however the role for this treatment remains unclear. Several recent trials combining MEK inhibition and immunotherapy have failed possibly because MEK inhibition can compromise T cell activation. Meanwhile the addition of CTLA4 blockade to PD1 inhibition appears to disproportionately benefit patients with non-T cell-inflamed tumors and potentially high-risk disease. For patients with high risk BRAF-mutant metastatic melanoma, further investigation of BRAF/MEK targeted and PD-1/CTLA-4 directed immunotherapy combination strategies remains a priority. **Methods:** This is an open label, multi-site, Phase 1/2 study of encorafenib (Enco) +/- binimetinib (Bini) + nivolumab (Nivo) + ipilimumab (Ipi) for the treatment of patients with unresectable or metastatic *BRAF*-mutated melanoma in high-risk cohorts (NCT04655157). An initial regimen confirming Phase I approach will be pursued on two schedules concurrently, with patients accruing equally to each group. Group 1 will receive 3mg/kg Nivo, and 1 mg/kg Ipi and 300mg Enco (12 participants, triple therapy) and Group 2 will receive 3mg/kg Nivo and 1mg/kg Ipi and 450mg Enco and 45mg Bini, (12 participants, quadruple therapy). Dose limiting toxicity (DLT) will be evaluated weeks 1-6. A recommended Phase II regimen (RP2R) [either triple or quadruple therapy] will be carried forward into two high risk metastatic disease cohort expansions of 30 participants each. Cohort 1 will include patients with symptomatic brain metastases, while cohort 2 will include patients with elevated LDH as well as either liver metastases OR bulky visceral disease (sum of longest diameters $>$ 44mm). Patients meeting criteria for cohorts 1 and 2 will be placed in cohort 1. Patients with symptomatic brain metastases will be included with an ECOG up to 2 and on $\leq$ 4mg of dexamethasone or equivalent. Continuous Bayesian toxicity monitoring will be used throughout to monitor DLT. Pre and on-treatment tumor biopsies will assess changes in the tumor microenvironment while peripheral blood ctDNA and T cell Ki67% changes will assess early response and immune activation during triplet and quadruplet therapy. Clinical trial information: NCT04655157. Research Sponsor: Bristol Myers Squibb.