LBA9500 **Oral Abstract Session**

Nivolumab plus relatlimab vs nivolumab alone for the adjuvant treatment of completely resected stage III–IV melanoma: Primary results from RELATIVITY-098.

Georgina V. Long, Paolo Antonio Ascierto, Jun Guo, Sunandana Chandra, Ahmad A. Tarhini, Eva Muñoz Couselo, Michele Del Vecchio, Andreia Cristina De Melo, Helen Gogas, Reinhard Dummer, Margaret K. Callahan, Dirk Schadendorf, Peter Koelblinger, Gaelle Quereux, Ioannis Thomas, Bohang Chen, Alicia Mun Yen Cheong, Patrick Djidel, Sonia Dolfi, Hussein A. Tawbi; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Peking University Cancer Hospital & Institute, Beijing, China; Northwestern University, Chicago, IL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Nacional Cancer Institute, Brazil, Rio De Janeiro, Brazil; National and Kapodistrian University of Athens, Athens, Greece; Department of Dermatology Universität Zürich, Zürich, Switzerland; Memorial Sloan Kettering Cancer Center, New York, NY; University of Essen and the German Cancer Consortium, Essen, Germany; Paracelsus Medical University, Salzburg, Austria; Nantes University Hospital, Skin Cancer Unit, Nantes, France; University of Tuebingen, Tuebingen, Germany; Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Uxbridge, United Kingdom; Bristol Myers Squibb, Boudry, Switzerland; The University of Texas MD Anderson Cancer Center, Houston, TX

LBA9501 **Oral Abstract Session**

Primary analysis of the EORTC-2139-MG/Columbus-AD trial: A randomized trial of adjuvant encorafenib and binimetinib versus placebo in high-risk stage II melanoma with a BRAF-V600E/K mutation.

Alexander Christopher Jonathan van Akkooi, Mario Mandala, Michal Kicinski, Anne-sophie Govaerts, Axel Hauschild, Piotr Rutkowski, Petr Arenberger, Paolo Antonio Ascierto, Piotr Tomczak, Gaelle Quereux, Federica De Galitiis, Caroline Dutriaux, Christoffer Gebhardt, Ellen Kapiteijn, Laurent Machet, Isabelle Klauck, Benoit Sansas, Paul Lorigan, Georgina V. Long, Alexander M. Eggermont; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Department of Medical Oncology, University of Perugia, Santa Maria Misericordia Hospital, Perugia, Italy; EORTC Headquarters, Brussels, Belgium; Department of Dermatology, University Hospital (UKSH), Kiel, Germany; Maria Skłodowska-Curie National Institute of Oncology Center, Warsaw, Poland; University Hospital Kralovske Vinohrady Prague and Charles University Third Medical Faculty, Prague, Czech Republic; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Pratia Poznań Medical Center, Poznan, Poland; Nantes University Hospital, Skin Cancer Unit, Nantes, France; Medical Oncology, Istituto Dermopatico Dell'immacolata, Rome, Italy; CHU de Bordeaux, Hôpital Saint André, Bordeaux, France; Department of Dermatology/Skin Cancer Center, University Medical Center Hospital Hamburg-Eppendorf, Hamburg, Germany; Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands; CHU de Tours - Hospital Trousseau, Cambray-Les-Tours, France; Pierre Fabre Medicament, Boulogne-Billancourt, France; Pierre Fabre, Toulouse, France; University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; Faculty of Medicine University Medical Center and Princess Máxima Center, Utrecht, Netherlands, and Comprehensive Cancer Center Munich and Technical University Munich & Ludwig Maximilian University, Munich, Germany

Neoadjuvant-adjuvant pembrolizumab in clinical stage IIB/C melanoma.

John Miura, Mohammad Saad Farooq, Phyllis A. Gimotty, Tara C. Mitchell, Ravi K. Amaravadi, Lynn M. Schuchter, Sheryl Mitnick, Xiaowei Xu, Alexander Chan Chi Huang, Michael A. Davies, Rodabe Navroze Amaria, Jason Alan Chesney, Roi Weiser, Jeffrey E. Gershenwald, Kelly McMasters, Giorgos Constantine Karakousis; University of Pennsylvania, Media, PA; University of Pennsylvania, Philadelphia, PA; University of Pennsylvania School of Medicine, Philadelphia, PA; Abramson Cancer Center, Philadelphia, PA; University of Pennsylvania Health System, Philadelphia, PA; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Melanoma Medical Oncology, Houston, TX; James Graham Brown Cancer Center, University of Louisville, Louisville, KY; Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Louisville, Louisville, KY; Division of Endocrine and Oncologic Surgery, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: Neoadjuvant immune checkpoint therapy has shown improvement in event-free survival outcomes in patients with resectable clinical stage III and IV melanoma. Whether there is benefit to neoadjuvant immune therapy in patients with clinical stage IIB/C melanoma is unknown. **Methods:** In a single arm multicenter investigator-initiated phase 2 trial, patients with clinical stage IIB/C melanoma received a single dose of neoadjuvant pembrolizumab (200 mg intravenously) 3 weeks prior to wide excision and sentinel lymph node (SLN) biopsy followed by 1 year adjuvant pembrolizumab every 3 weeks or until unacceptable toxicity or disease progression. Primary endpoint was SLN positivity rate. A sample size of 63 patients had 80% power detect a 50% difference when compared to a predetermined historical SLN positivity rate in treatment naïve patients (25% Stage IIB and 40% Stage IIC) weighted by proportion of clinical tumor stage in eligible study patients. Secondary endpoint included recurrence-free survival. Safety outcomes, including overall toxicity and immune related adverse events, were also assessed. **Results:** Of 63 evaluable patients (33 IIB; 30 IIC at initial biopsy), the SLN metastasis rate in the neoadjuvant study group was 27%. 28 patients (44%) had residual primary tumor after single dose pembrolizumab; 4 patients had their primary tumors upstaged to IIC. Compared to a SLN metastasis rate in a historical treatment- naïve cohort based on tumor staging at wide excision (33.1%), there was a 18% reduction in SLN positivity rate in the neoadjuvant group, although this was not statistically significant ($p = 0.302$). In a subgroup analysis, stage IIC patients in the neoadjuvant study group had a SLN metastasis rate of 16.7% versus 40% ($p = 0.009$) based on initial biopsy and 23.5% versus 40% ($p = 0.0499$) based on primary tumor staging at wide excision. With median follow-up of 20.4 months, the 2-year recurrence free-survival in the study group was 84% with median time to recurrence ($n = 10$) of 9.9 months. Overall treatment-related grade 3/4 adverse events were 14 (22%) with 9 (14%) immune-related adverse events; there was no delay in definite surgery secondary to neoadjuvant treatment. **Conclusions:** Rate of SLN metastasis among patients with clinical stage IIB/C melanoma undergoing neoadjuvant pembrolizumab did not differ significantly compared to expected historical rates in treatment-naïve patients; however, in a secondary subgroup analysis among patients with clinical stage IIC disease, a decrease in SLN positivity rate was noted. Neoadjuvant therapy in clinical stage IIB/C was safe and feasible, with no significant delay in surgery or new or unexpected toxicities noted in these patients. Translational studies are under way, including flow cytometric and transcriptional studies, that may reveal immunologic determinants of efficacy versus resistance. Clinical trial information: NCT03757689. Research Sponsor: Merck; U.S. National Institutes of Health.

9503 Oral Abstract Session

NeoACTIVATE arm C: Phase II trial of neoadjuvant atezolizumab and tiragolumab for high-risk operable stage III melanoma.

Tina J. Hieken, David Zahrieh, Thomas J. Flotte, Roxana Stefania Dronca, Evidio Domingo-Musibay, Garth D. Nelson, Carrie Strand, Lisa A. Kottschade, Heather N. Montane, Mara Piltin, Ruqin Chen, Robert R. McWilliams, James W. Jakub, Samir Khariwala, Arkadiusz Z. Dudek, Jeffrey Johnson, Svetomir Markovic, Anastasios Dimou, Kendall Tasche, Matthew Stephen Block; Mayo Clinic, Rochester, MN; Mayo Clinic, Jacksonville, FL; Department of Oncology, University of Minnesota, Minneapolis, MN; Mayo Clinic Florida, Jacksonville, FL; Division of Medical Oncology, Mayo Clinic Rochester, Rochester, MN; University of Minnesota Physicians, Minneapolis, MN; Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN; Department of Oncology, Mayo Clinic, Rochester, MN

Background: Neoadjuvant ± adjuvant immunotherapy improves event-free survival relative to adjuvant immunotherapy alone for patients with high-risk resectable stage III melanoma. However, the optimal regimen balancing efficacy and tolerability is not known. T-cell immunoglobulin and ITIM domain (TIGIT) is a promising immune checkpoint but its therapeutic potential in stage III melanoma is underexplored. **Methods:** In this phase II trial, patients with resectable, macroscopic stage III melanoma received four 21-day neoadjuvant cycles of 1200mg IV atezolizumab (atezo, anti-PD-L1) + 600mg IV tiragolumab (tira, anti-TIGIT), followed by therapeutic lymph node dissection (TLND) and eight 21-day adjuvant cycles of 1200mg IV atezo. Primary endpoints were pathologic response (of all patients initiating neoadjuvant therapy) and recurrence-free survival (RFS) from the time of TLND in patients who were operated on per protocol and received adjuvant therapy. Secondary endpoint was adverse events (AEs); exploratory endpoints included event-free survival (EFS) and distant metastasis-free survival (DMFS). **Results:** Thirty-four patients, median age 59 years, were accrued and initiated neoadjuvant atezo/tira. 76.5% had >1 metastatic lymph node involved at baseline and 73.5% presented with Stage IIIC disease. All 34 patients were evaluable for AEs, pathologic response and EFS. Four patients were diagnosed with metastatic disease during neoadjuvant treatment, while 30 had TLND per protocol and 28 received adjuvant treatment and were evaluable for RFS and DMFS. Major pathologic responses (MPR, ≤10% viable tumor) were observed in 16/34 patients (47.1%, Table). With 19.9 months median follow-up from registration, 12-month EFS was 72.0% (95% CI 57.9 to 89.5%). With 16 months median follow-up from operation, 12-month RFS was 73.3% (n=28, 95% CI 56.9 to 94.5%), while 12-month DMFS was 86.0% (n=28, 95% CI 72.2 to 100%). In the 16 patients with an MPR, 2 did not receive adjuvant treatment and were followed for 33.3 and 10.8 months without recurrence/death. In the remaining 14 patients, 12-month RFS and 12-month DMFS were both 91.7% (95% CI 77.3 to 100%). 5 patients (14.7%) experienced any grade 3+ AE with 2 (5.9%) at least possibly related to the neoadjuvant regimen. **Conclusions:** Among patients with high-risk resectable stage III melanoma, neoadjuvant atezo/tira was a promising regimen with a favorable safety profile and warrants further study. Identification of predictive biomarkers will allow for optimization of neoadjuvant therapy for individual patients. Clinical trial information: NCT03554083. Research Sponsor: Stand Up to Cancer-Genentech; SU2C-AACR-CT1017; Mayo Clinic Center for Clinical and Translational Science; cCATS Award 92541640-2020/Mayo Clinic.

Pathologic response.

	N=34
Major Pathologic Response	16 (47.1%)
Pathologic complete response (no viable tumor)	13 (38.2%)
Near-pathologic complete response (0.1−10% viable tumor)	3 (8.8%)
Pathologic partial response (>10.0−50% viable tumor)	2 (5.9%)
Pathologic non-response (>50% viable tumor)	12 (35.3%)
No per protocol operation	4 (11.8%)

LBA9504 **Oral Abstract Session**

Randomized phase II study of neoadjuvant (neoadj) anti-PD-1 dostarlimab (D) vs. D + anti-TIM-3 cobolimab (C) in high-risk resectable melanoma (mel) (NEO-MEL-T): Primary analysis.

Meghan Mooradian, Arivarasan Karunamurthy, Hong Wang, Elizabeth Iannotti Buchbinder, Suthee Rapisuwon, Justine Vanessa Cohen, Geoffrey Thomas Gibney, Ryan J. Sullivan, Jason J. Luke, Yana G. Najjar, John M. Kirkwood, Hassane M. Zarour, Diwakar Davar; Massachusetts General Hospital, Marblehead, MA; University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; University of Pittsburgh, Pittsburgh, PA; Dana-Farber Cancer Institute, Boston, MA; Washington Cancer Institute/ Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; Lombardi Comprehensive Cancer Center, Washington, DC; Massachusetts General Hospital Cancer Center, Boston, MA; UPMC Hillman Cancer Center, Pittsburgh, PA

LBA9505 **Oral Abstract Session**

A phase II randomized study of neoadjuvant pembrolizumab (P) alone or in combination with vidutolimod (V) in high-risk resectable melanoma: ECOG-ACRIN EA6194.

Ahmad A. Tarhini, Sandra J. Lee, Diwakar Davar, Craig L. Slingluff Jr., Jane Messina, Gary Irvin Cohen, G. Paul Wright, Andrew Stewart Poklepovic, Yana G. Najjar, Jessica A. Cintolo-Gonzalez, Jose Lutzky, Elizabeth Mary Gaughan, Janice M. Mehnert, Jedd D. Wolchok, John M. Kirkwood; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Dana-Farber Cancer Institute, Boston, MA; UPMC Hillman Cancer Center, Pittsburgh, PA; University of Virginia, Charlottesville, VA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Cancer Ctr at GBMC, Pikesville, MD; Corewell Health/Michigan State University, Grand Rapids, MI; Virginia Commonwealth University Health System, Richmond, VA; University of Vermont Medical Center, Burlington, VT; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Perlmutter Cancer Center of NYU Langone Health/NYU Grossman School of Medicine, New York, NY; Weill Cornell Medical College, New York, NY

DREAMseq: A phase III trial of treatment sequences in BRAFV600-mutant (m) metastatic melanoma (MM)—Final clinical results.

Michael B. Atkins, Sandra J. Lee, Bartosz Chmielowski, Ahmad A. Tarhini, Gary Irvin Cohen, Geoffrey Thomas Gibney, Thach-Giao Truong, Diwakar Davar, Joe Stephenson, Brendan D. Curti, Joanna M. Brell, Kari Lynn Kendra, Alexandra Ikeguchi, Zihe Song, Samantha Guild, Jedd D. Wolchok, Antoni Ribas, John M. Kirkwood; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Dana-Farber Cancer Institute, Boston, MA; University of California Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Cancer Ctr At GBMC, Pikesville, MD; Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; Cleveland Clinic, Cleveland, OH; UPMC Hillman Cancer Center, Pittsburgh, PA; NCORP of the Carolinas, Greenville, SC; Earle A Chiles Research Institute, Portland, OR; Department of Hematology and Oncology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH; Ohio State University Comprehensive Cancer Center, Hilliard, OH; The University of Oklahoma Medical Center, Oklahoma City, OK; AIM at Melanoma, San Rafael, CA; Weill Cornell Medical College, New York, NY; UCLA, Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: The DREAMseq trial compared efficacy and toxicity of the sequence of nivolumab/ipilimumab (N/I) followed by dabrafenib/trametinib (D/T) to the reverse sequence in patients (pts) with BRAFV600m MM. In 9/2021, with 59% of pts 2+ years (yr) from enrollment, the DSMC and NCI CTEP recommended halting the trial and releasing data that showed a 20% difference in 2-yr OS (72% vs 52%) favoring the N/I first sequence. Here we update data to median ~5 yr from entry and report secondary analyses including time to CNS relapse and percent unconfirmed responses (ucOR). **Methods:** Eligible pts with untreated BRAFV600m MM were stratified by ECOG Performance Status 0 or 1 and LDH, and randomized 1:1 to Step 1 treatment with either N/I (Arm A) or D/T (Arm B) and at disease progression (PD) were eligible for Step 2 alternate therapy, D/T (Arm C) or N/I (Arm D). Imaging was done at baseline and q12 weeks (wks). The primary endpoint was 2-yr OS. Secondary endpoints included: 3-yr OS, efficacy (PFS, ORR and DOR) and toxicity. **Results:** 267 out of 300 proposed pts were enrolled (135 Arm A; 132 Arm B). As of 7/23/24, median follow-up of 58 months (mo) (range:0-101), 30 pts had switched to Arm C and 52 to Arm D. 2-yr OS for those assigned to Arm A was 68.3% (95% CI: 60.8-76.9) and for Arm B 54.1% (95% CI: 46.1-63.7%) (log-rank $p < 0.01$). 3 and 5-yr OS by sequence and 2, 3 and 5-yr PFS for initial arms, and median PFS, ORR and DOR for all arms are shown in Table. There were 125 deaths (Arm A-C: 47; Arm B-D:78). 76% of responders in Arm A and 24% in Arm B remain in response. At 12 wks, 59 pts on Arm A and 85 on Arm B had RECIST PR of which 10 (16.9%) and 35 (41.2%), respectively were ucOR by wk 24. CNS was the first site of PD in 24 pts on Arm A and 44 pts on Arm B. Median time to CNS PD: Arm A 12.2 mo (0.7-46.5); Arm B 8.4 mo (1.3-78.1) ($p < 0.01$). **Conclusions:** At nearly 5 yr median f/up, the N/I first treatment sequence continues to show superior efficacy over the D/T first sequence for treatment-naïve BRAFV600m MM with a near doubling (30% absolute difference) in 5-yr OS and a tripling of 5-yr PFS. While confirmed ORR were similar between Arms A and B, shorter DOR and more ucOR and more and earlier CNS PD were seen with initial D/T contributing to its worse efficacy. Clinical trial information: NCT02224781. Research Sponsor: This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health:; U10CA180820, U10CA180794, U10CA180821, U10CA180868, U10CA180888, UG1CA189953, UG1CA233184, UG1CA233193, UG1CA233196, UG1CA233234, UG1CA233290, UG1CA233331, and UG1CA239758.

Secondary Endpoint (95% CI)	Arm A to C (n=135)	Arm B to D (n=132)	Log-rank p
3 yr OS rate	65.6% (57.3, 73.9)	44.8% (36.7, 54.6)	p<0.01
5 yr OS rate	63.3% (55.4, 72.3)	33.9% (25.9, 44.3)	
2 yr PFS rate	Arm A	Arm B	
	50.8% (42.8, 60.3)	22.9% (16.5, 31.7)	p<0.01
3 yr PFS rate	45.0% (37.0, 54.8)	15.9% (10.5, 24.0)	
5 yr PFS rate	39.4% (31.3, 49.5)	12.8% (7.9, 20.7)	
Median PFS (mo)	Arm A	Arm B	
	26.7 (11.2-47.3)	8.5 (8.1-12.6)	
	Arm C (n=30)	Arm D (n=52)	
	11.2 (9.5, 22.3)	5.9 (2.9, 22.4)	
ORR	Arm A (n= 132)	Arm B (n=131)	
	51.5% (42.7, 60.3)	51.1% (42.3, 60.0)	
	Arm C (n=30)	Arm D (n= 52)	
	70% (37.4, 74.5)	46.2% (32.2, 60.5)	
Median DOR (mo)	Arm A (n=68)	Arm B (n=67)	<0.01
	Not reached	15.5 (11.2, 23.5)	
	Arm C (n=17)	Arm D (n=20)	p=0.03
	14.7 (8.2, NR)	45.2 (19.5, NR)	

LBA9507 **Oral Abstract Session**

A randomized phase 2 trial of encorafenib + binimetinib + nivolumab vs ipilimumab + nivolumab in BRAFV600-mutant melanoma brain metastases: SWOG S2000 (NCT04511013).

Zeynep Eroglu, James Moon, Yana G. Najjar, Rupesh Kotecha, Michael Wu, Vadim Spektor, Nikhil I. Khushalani, Larissa A. Korde, Elad Sharon, Kenneth F. Grossmann, John M. Kirkwood, Jedd D. Wolchok, Sapna Pradyuman Patel, Hussein A. Tawbi; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; SWOG Statistical Center, Seattle, WA; UPMC Hillman Cancer Center, Pittsburgh, PA; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Columbia University Irving Medical Center, New York, NY; National Cancer Institute, Bethesda, MD; Providence Cancer Institute, Portland, OR; Weill Cornell Medical College, New York, NY; University of Colorado Comprehensive Cancer Center, Aurora, CO; The University of Texas MD Anderson Cancer Center, Houston, TX

LBA9508 **Oral Abstract Session**

Comparison of 1 year versus minimum 2 years of anti-PD1-based immunotherapy as first-line treatment for metastatic melanoma: Results of the DANTE phase III trial.

Sarah Danson, Michelle Collinson, Elizabeth Ruth Plummer, Christian H.H. Ottensmeier, Shobha Silva, Jane Hook, Brindley Sonal Hapuarachi, Matthew Wheater, Miranda Payne, Olabode Oladipo, Ashita Marie Waterston, Galina Velikova, Ferdia Aidan Gallagher, David M. Meads, Sue E. Bell, Natasha Greatorex, Eszter Katona, Janine Bestall, Susanna Daniels, Philippa Gail Corrie; Cancer Therapeutics, Division of Clinical Medicine, University of Sheffield; Department of Oncology, Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, United Kingdom; Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom; Newcastle University Centre for Cancer, Newcastle upon Tyne, and Sir Bobby Robson Cancer Trial Research Centre, Freeman Hospital, the Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; University of Liverpool, Liverpool, United Kingdom; The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom; St. James's University Hospital, Leeds, United Kingdom; Cancer Therapeutics, Division of Clinical Medicine, University of Sheffield, Sheffield, United Kingdom; Southampton Oncology Centre, Southampton, United Kingdom; Churchill Hospital, Oxford, United Kingdom; Northern Ireland Cancer Centre, Belfast, United Kingdom; The Beatson Cancer Centre, Glasgow, United Kingdom; Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, United Kingdom; Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; University of Leeds, Leeds, United Kingdom; Leeds Institute of Health Sciences, University of Leeds, Leeds, United Kingdom; Melanoma Focus, Cambridge, United Kingdom

9509 Rapid Oral Abstract Session

A first-in-human study of DYP688, an antibody drug conjugate delivering a direct Gq/11 inhibitor, in patients with metastatic uveal melanoma (MUM) and other GNAQ/11 mutant melanomas.

Matteo S. Carlino, Reinhard Dummer, Tanja Gromke, Jessica Cecile Hassel, Ellen Kapiteijn, Damien Kee, Sophie Piperno-Neumann, Egle Ramelyte, Alexander Noor Shoushtari, Ryan J. Sullivan, Alexander Z Wei, Anne-Marie Duggan, Mary Elizabeth Ising, Pedro Milanez-Almeida, Thiruvamoor Ramkumar, Aimee Reynolds, Sherif Sharaby, Padmaja Yerramilli-Rao, Emiliano Calvo; Sydney Medical School, Faculty of Medicine and Health Sciences, The University of Sydney, Camperdown and Melanoma Institute Australia, Sydney, and Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Westmead, NSW, Australia; Department of Dermatology Universität Zürich, Zürich, Switzerland; University Hospital Essen, West German Cancer Center, Essen, Germany; University Hospital Heidelberg, Heidelberg, Germany; Leiden University Medical Center, Leiden, Netherlands; Peter Mac Callum, Heidelberg, VIC, Australia; Institut Curie, Paris, France; Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital Cancer Center, Boston, MA; Columbia University Irving Medical Center, New York, NY; Novartis Ireland Ltd, Ireland, United Kingdom; Novartis Pharmaceutical Corporation, Basking Ridge, NJ; Biomedical Research, Novartis, Cambridge, MA; Novartis Institutes for BioMedical Research, Cambridge, MA; Novartis, Cambridge, MA; Biomedical Research, Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Institutes for BioMedical Research, Inc., Cambridge, MA; START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain

Background: GNAQ/11 mutations occur in up to 95% of uveal melanomas (UM) and a subset of non-uveal melanomas. Cell surface PMEL17 (gp100) is highly and broadly expressed in melanoma (including UM). SDZ475 (FR900359) is a potent GNAQ/11 inhibitor, however in vivo toxicity has precluded clinical development. DYP688 is an antibody drug conjugate that binds to PMEL17 to deliver the payload SDZ475. **Methods:** This first-in-human, open-label, multicenter, single-arm study (NCT05415072) of DYP688 in patients (pts) with MUM and other GNAQ/11 mutant melanomas aimed to evaluate safety and tolerability, determine recommended dose(s) (RDs) of DYP688 (primary objective), and evaluate antitumor activity, pharmacokinetics (PK), and immunogenicity (secondary objectives). Here we present data from the ongoing Phase I dose-escalation. **Results:** As of 25 Oct 2024, 66 pts were treated with DYP688 at 4 (n=5), 8 (n=12), 12 (n=13), 16 (n=14), and 24 (n=11) mg/kg biweekly (Q2W) and at 12 (n=5) and 16 (n=6) mg/kg once weekly (QW) in 28-day cycles. Tumor types included MUM (n=60) and non-MUM (n=6). Of the 66 treated pts, 60 (90.9%) had prior antineoplastic therapy; 38 (57.6%) received ≥2 lines, and 22 (33.3%) received prior tebentafusp. The majority (n=57, 86.4%) of pts had liver metastases and elevated LDH (n=43, 65.25%) at baseline. Preliminary PK demonstrated a nearly dose-proportional exposure of total monoclonal antibody and active conjugated payload. Most treatment-related adverse events (TRAEs) were grade ≤2 with 4 grade 3 events: hypotension, hypercalcemia, anemia, and increased GGT. One dose limiting toxicity was reported (grade 3 hypotension at 24mg/kg Q2W). Most common TRAEs (all grades/doses, >15%) were hypercalcemia (22.7%), dry mouth (19.7%), fatigue (18.2%) and peripheral edema (16.7%). At data cutoff, 27 (40.9%) pts remained on study treatment and 39 (59.1%) pts had discontinued, mainly due to disease progression (PD) and none due to AEs. Of the 55 pts treated at doses ≥8 mg/kg Q2W who were eligible for RECIST v1.1 evaluation, confirmed objective responses were seen in 12 (21.8%) pts with 1/12 at 8 mg/kg (Q2W), 3/13 (1 complete response) at 12 mg/kg (Q2W), 5/8 at 16 mg/kg (Q2W), 2/5 at 12 mg/kg (QW) and 1/6 at 16 mg/kg (QW), with evidence of deepening response over time. Best response of PD was seen in 6/55 (10.9%) pts and stable disease in 35/55 (63.6%) pts. Median (range) duration of treatment by Kaplan Meier was 7.0 (<1 – 20.7) months. Analysis of mutational profiles from tissue and circulating tumor DNA is ongoing. **Conclusions:** DYP688 shows favorable safety and tolerability at all doses tested and promising preliminary clinical efficacy at doses ≥ 12mg/kg Q2W; the RDs for dose optimization are yet to be declared and dose exploration is ongoing. Clinical trial information: NCT05415072. Research Sponsor: Novartis Pharmaceutical Corporation.

9510 Rapid Oral Abstract Session

A phase II study of the interleukin-6 (IL-6) receptor blocking antibody sarilumab (Sari) in combination with ipilimumab (Ipi), nivolumab (Nivo) and relatlimab (Rela) in patients with unresectable stage III or stage IV melanoma.

Janice M. Mehnert, Inderjit Mehmi, Judith D. Goldberg, Maya Dimitrova, Perla Arriola, Amrutesh Puranik, Teruyuki Mizutani, Stanzin Idga, Xiaochun Li, Benjamin A. Levinson, Justine Vanessa Cohen, Elizabeth Iannotti Buchbinder, Donald P. Lawrence, Alissa Kalyan, Morgan Simons, Jonah Michael Levine, F. Stephen Hodi, Ryan J. Sullivan, Omid Hamid; Perlmutter Cancer Center of NYU Langone Health/NYU Grossman School of Medicine, New York, NY; The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA; New York University Grossman School of Medicine, New York, NY; NYU Langone Medical Center, New York, NY; Laura and Isaac Perlmutter Cancer Center, New York, NY; Laura And Isaac Perlmutter Cancer Center, New York, NY; NYU Langone Grossman School Of Medicine, New York, NY; NYU Grossman School of Medicine, Department of Population Health, Division of Biostatistics, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; Department of Medicine, Laura & Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY; NYU Grossman School of Medicine, New York, NY; Division of Medical Oncology, Massachusetts General Hospital, Boston, MA

Background: Combination immune checkpoint inhibitor regimens, especially those utilizing anti-CTLA-4 blockade, demonstrate higher response rates compared with single agent anti-PD-1 therapy but also increased rates of immune related adverse events (irAEs). IL-6, a key cytokine in driving inflammatory and autoimmune responses, is a compelling target to reduce irAEs through the use of IL-6 receptor (IL-6R) inhibitors. We conducted a clinical trial of 1L Nivo, Rela, and Ipi combined with the IL-6R inhibitor Sari in patients with advanced melanoma. **Methods:** 33 patients with advanced stage III/IV melanoma were treated in a single arm phase II trial. Patients received Nivo/Rela 480 mg/160 mg Q4W, Ipi 1 mg/kg Q8W and Sari 200mg q2 weeks for 12 doses over 24 weeks followed by maintenance Nivo/Rela 480 mg/160 mg Q4W and Ipi 1 mg/kg Q8W. Prior adjuvant immunotherapy was allowed if $>$ 6 months before enrollment. Patients with controlled brain metastases could enroll. The co-primary endpoints were rate of grade (gr) 3-5 irAEs and antitumor activity defined by RECIST best overall response rate at 24 weeks. With 33 patients, a difference of $\geq$ 22% from the known irAE rate of Nivo, Rela, and Ipi could be detected using a binomial test (2-sided alpha = 0.05, 80% power). BORR was estimated with an exact 95% Clopper Pearson confidence interval. Circulating IL-6 signaling mediators were measured over time in 14 patients using Luminex assays. **Results:** 33 patients (40% F, 60% M, PS 0-1, median age 63) were treated. Median follow-up was 9.8 months (95% CI: 8.5, 12.6 months; data lock, 12/12/24). 3% had acral and 9% mucosal melanoma. 24% had $>$ M1c disease and 39% elevated LDH. BRAF status, known for 81% of patients, was positive in 26%. BORR at 24 weeks was 63.6% (95% CI: 45.1%, 79.6%). Median PFS and OS were not reached (25^{th} percentile for PFS = 8.3 (95% CI: 2.77, NA) months). Median treatment duration was 28 weeks and 9% discontinued therapy for toxicity. At 24 weeks 12.1% (n = 4) experienced $>$ gr 3/4 irAEs, significantly lower than the expected known irAE rate (2-sided p = 0.0007, 95% CI: 12.1%-28.2%). 27% (n = 9) had gr 3/4 toxicity over study duration; 93.9% (n = 31) had any grade irAE. Circulating IL-6Ra and IL-4 were significantly reduced at Cycle 2 ($P < 0.05$). **Conclusions:** Nivo, Rela, Ipi, + Sari demonstrated encouraging efficacy and tolerability. At 24 weeks, 63.6% BORR and 12.1% gr 3/4 irAE rate were observed. 2 patients had gr 4 toxicity; no gr 5 events were reported. These results compare favorably with published combination regimens including CTLA-4 blockade. Decreases in lL-6Ra and the inflammatory marker IL-4 observed post-treatment will be evaluted in a larger cohort of samples. An ongoing randomized cohort of Nivo + Rela + Ipi +/- Sari will further define the impact of IL-6R blockade on clinical outcomes in metastatic melanoma. Clinical trial information: NCT05428007. Research Sponsor: Bristol Meyers Squibb; Regeneron.

9511 Rapid Oral Abstract Session

Clinical outcomes of the DIET study: A randomized controlled phase 2 trial of a high fiber diet intervention (HFDI) in patients with melanoma receiving immune checkpoint blockade (ICB).

Yufan Qiu, Nazli Dizman, Yan Jiang, Margaux Robert, Rachel Farias, Erma J. Levy, Cindy Hwang, Jian Wang, Michael K.K. Wong, Sapna Pradyuman Patel, Alexandra Ikeguchi, Isabella Oliva Glitz, Adi Diab, Hussein A. Tawbi, Rodabe Navroze Amaria, Michael A. Davies, Nadim J. Ajami, Jennifer Ann Wargo, Carrie Daniel-MacDougall, Jennifer Leigh McQuade; The University of Texas MD Anderson Cancer Center, Houston, TX; Roswell Park Comprehensive Cancer Center, Buffalo, NY; University of Colorado Comprehensive Cancer Center, Aurora, CO

Background: Dietary fiber intake is associated with response to ICB in melanoma. HFDIs favorably modulate the microbiome in non-cancer populations and in preclinical models. However, whether diet intervention can favorably modulate the microbiome and immune response in cancer patients is unknown. We conducted a proof-of-principal randomized trial of a fully controlled feeding study comparing HFDI with healthy control diet in melanoma patients receiving ICB. The primary objective was to establish the effects of HFDI on the structure and function of the gut microbiome. Here we report an exploratory objective of cancer-specific outcomes by arm. **Methods:** Patients initiating ICB treatment for melanoma-were randomized (2:1) to either HFDI (30 g/d fiber ramped-up biweekly via whole foods to 50 g/d) or healthy control diet (20 g/d fiber). Diets in both arms met cancer prevention guidelines, were isocaloric and macronutrient-controlled, such that participants were provided all calorie-containing meals/snacks and met weekly with the dietitian for the study duration (up to 10 weeks). Objective response rate (ORR, per RECIST 1.1), pathological response rate (per INMC), progression-free survival (PFS), event-free survival (EFS, defined as the time from treatment initiation to disease progression, recurrence or death), recurrence rate (RR), recurrence-free survival (RFS) and immune-related adverse event (IRAE) rates were assessed and compared across arms. **Results:** 45 patients were randomized, of which 43 (F/M 22/21, median age 57 years, 79% cutaneous) initiated ICB and diet intervention: 28 in the HFDI arm and 15 in the control arm. ICB was administered in adjuvant, neoadjuvant and unresectable setting in 19, 12, and 12 patients, respectively. ICB regimens include pembrolizumab or nivolumab monotherapy (n = 19), ipilimumab + nivo (n = 16), and nivo + relatlimab (n = 7). At the time of data cut-off, October 2024, the median follow-up was 22.6 months (95% CI: 22.05-24.95 months). In the combined neoadjuvant/unresectable cohort (n = 24), ORR was 77% (HFDI) and 29% (control, p = 0.06). In the neoadjuvant cohort (n = 12), pathological complete response rate was 57%(HFDI) vs 50% (control, p = 1.0). Median EFS was not reached (HFDI) versus 20 months (control, p = 0.03). In the adjuvant cohort (n = 19), at a median follow-up of 27.6 months, RR was 14% (HFDI) versus 33% (control, p = 0.56). Median RFS was not reached (HFDI) versus 27.8 months (control, p = 0.49). Any grade IRAEs were observed in 71.4% of the patients in the HFDI arm versus 93.3% in the control arm (p = 0.13). Grade ≥3 IRAE rates were 28.6% and 40.0% in the HFDI and control arms (p = 0.51), respectively. **Conclusions:** Our study suggests potential benefits of HFDI on clinical outcomes and toxicity profile with ICB, warranting further study in Phase III trials powered for disease outcomes. Clinical trial information: NCT04645680. Research Sponsor: None.

9512 Rapid Oral Abstract Session

Neoadjuvant camrelizumab plus apatinib and temozolomide for resectable stage II/III acral melanoma: The CAP 03-NEO trial.

Lili Mao, Caili Li, Jie Dai, Xiaoting Wei, Junjie Gu, Yu Du, Yan Kong, Xinan Sheng, Chuanliang Cui, Zhihong Chi, Bin Lian, Bixia Tang, Xieqiao Yan, Xuan Wang, Siming Li, Li Zhou, Juan Li, Xiaowen Wu, Jun Guo, Lu Si; Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China; Department of Genitourinary Oncology, 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; Peking University Cancer Hospital & Institute, Beijing, China

Background: The CAP 03 study demonstrated significant efficacy for camrelizumab combined with apatinib and temozolomide as first-line therapy for advanced acral melanoma (AM), achieving a 64.0% objective response rate and a median progression-free survival of 18.4 months. SWOG1801 and NADINA trials suggested that neoadjuvant therapy may provide greater benefits than adjuvant therapy in melanoma. CAP 03-NEO explores the efficacy and safety of this triple-drug regimen as neoadjuvant therapy in patients (pts) with resectable stage II/III AM. **Methods:** This two-stage clinical trial (ClinicalTrials.gov identifier: NCT05512481) aimed to enroll 60 pts with resectable stage II/III AM aged 18–75 years. In stage 1, 30 pts received two 4-week cycles of neoadjuvant camrelizumab (200 mg intravenously every 2 weeks), apatinib (250 mg orally once daily), and temozolomide (200 mg/m^2 intravenously daily on days 1–5 of each cycle), followed by surgery and 15 cycles of adjuvant camrelizumab (200 mg every 3 weeks). The primary endpoint was pathological complete response (pCR). Secondary endpoints included event-free survival (EFS), overall survival, and safety. Based on pathologic non-response (pNR) rate and risk-benefit assessment, stage 2 extended enrollment to an additional 30 pts receiving the same treatment. **Results:** As of December 2024, all 30 pts in stage 1 were enrolled, with a median follow-up of 18.5 months. The median age was 54 years (IQR: 41–61). Of 28 pts undergoing surgery, 16 (57.1%) achieved any pathological response, including 7 (25.0%) with pCR, 5 with near pCR, and 4 with partial pathologic response (pPR). Additionally, 12 pts (42.9%) achieved major pathological response (MPR), which includes both pCR and near-pCR. Surgery was canceled for two pts due to personal reasons and new metastatic disease. Among stage II pts, 3 achieved pCR, 1 achieved pPR, and the pNR was 64%. Among stage III pts, 4 achieved pCR, 5 near PCR, and 3 pPR, with pNR of 29.4%. The median EFS has not been reached, with a 12-month EFS rate of 74.1% (95% CI: 53.1-86.7%). The most common adverse events (AEs) were increased blood bilirubin (11, 37%), decreased white blood cell count (9, 30%), and constipation (8, 27%), with no grade 4-5 AEs observed. Neoadjuvant therapy did not increase surgical complications. **Conclusions:** Stage 1 results of CAP 03-NEO demonstrated the potential of neoadjuvant camrelizumab, apatinib and temozolomide in pts with resectable stage II/III AM. The pNR result support advancing to stage 2 to further assess the efficacy and safety of this regimen in pts with stage III disease. Clinical trial information: NCT05512481. Research Sponsor: None.

9513 Rapid Oral Abstract Session

Single dose of neoadjuvant ipilimumab and nivolumab in resectable melanoma with CD8+ cell imaging: Interim results of the C-IT Neo trial.

Sarah E. Lochrin, Cecilia Lezcano, James Russell, Jeeban Paul Das, Hannah L. Kalvin, James William Smithy, Shutian Ruan, Alexander Noor Shoushtari, Parisa Momtaz, Monica F. Chen, Claire Thant, Danielle M. Bello, Edmund Bartlett, Mary Susan Brady, Charlotte Eielson Ariyan, Katherine Panageas, Neeta Pandit-Taskar, Michael A. Postow; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

Background: Neoadjuvant (neoadj) immune checkpoint blockade (ICB) is standard of care for patients (pts) with resectable stage III/IV melanoma. A single ICB dose induces substantial peripheral immune activation and 1 dose of neoadj pembrolizumab has promising activity. The efficacy of 1 dose of combination ICB is unknown and clinically important to describe given the toxicity of sequential combination ICB. **Methods:** In this phase II single-arm trial, pts with resectable stage IIIB-IV melanoma received 1 dose of neoadj nivolumab (nivo) 1mg/kg and ipilimumab (ipi) 3mg/kg 4 weeks prior to resection. The primary endpoint is major pathologic response (MPR), defined as pathologic complete response (pCR) or near CR (≤10% viable tumor). Using a Simon minimax two-stage design, MPR < 30% is deemed not promising and > 50% promising; positive if >12 MPR in 28 pts. Secondary endpoints were response rate (RECIST 1.1), recurrence free survival (RFS), and safety. CD8-PET imaging was done pre-ICB and pre-surgery, using ^{89}Zr-radiolabeled crefmirlimab to evaluate association with MPR. Autoradiography and CD8 cell infiltrate by IHC were used to verify the on-target binding of crefmirlimab in surgical specimens. **Results:** Stage I successfully met the interim efficacy threshold with 5 of 12 pts demonstrating an MPR, thus advancing to stage II. Here we report interim results of the 19 pts enrolled by data cut-off 01/02/2025. Baseline stages were IIIB (53%, n = 10), IIIC (42%, n = 8) and IV (5%, n = 1); 80% cutaneous, 10% acral and 10% unknown primary melanoma. An MPR was observed in 53% (95% CI: 29,76) of pts (n = 10, 7 pCR, 3 near pCR), partial pathologic response (PR) in 21% (n = 4), and non-response in 26% (n = 5). Of the 18 evaluable, RECIST response was 28% (n = 5, all PR), 61% (n = 11) had stable disease, and 11% (n = 2) progressive disease (PD). The rate of grade >3 treatment-related adverse events (TRAE), in neoadj and adjuvant setting, was 11% (n = 2); 1 pt was hospitalized with adrenal insufficiency, no grade 5 events occurred on study. All pts proceeded to surgery with median time to surgery of 29 days (IQR 26,31). 14 pts (74%) received adjuvant therapy; 13 anti-PD-1 and 1 BRAF targeted therapy. Median follow-up was 16 months (IQR 8;23) and 12-month RFS from surgery was 91% (95% CI: 75, 100). Of the 3 pts with recurrent or progressive disease; 0 had an MPR and 2 died from progressive melanoma. CD8-PET was completed in 19 pts pre-ICB and 17 pts pre-surgery. SUVmax pre-ICB, pre-surgery and the percent change over-time was not significantly associated with MPR. CD8-PET tracer evaluation by autoradiography correlated with CD8+ cell infiltrate on IHC by pathologist assessment. **Conclusions:** C-IT-Neo is the first study evaluating a single dose of combination ICB in the neoadjuvant setting. Interim results show one dose has low grade 3+ TRAE and high efficacy with MPR of 53%. The trial is actively enrolling, with ongoing analysis of CD8-PET imaging and immune biomarkers. Clinical trial information: NCT05289193. Research Sponsor: Melanoma Research Alliance; ImaginAb.

9514 Rapid Oral Abstract Session

A phase II study of neoadjuvant lenvatinib plus pembrolizumab in Merkel cell carcinoma.

Andrew Scott Brohl, Vernon K. Sondak, Evan John Wuthrick, Youngchul Kim, Zeynep Eroglu, Joseph Markowitz, Ahmad A. Tarhini, Wenyi Fan, Justin Martin, Lymon Sneed, Matthew Perez, Amod Sarnaik, Michael Harrington, Rogerio Izar Neves, Ricardo Jorge Gonzalez, Wayne Cruse, Jonathan S. Zager, Kenneth Yee Tsai, Nikhil I. Khushalani; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Given the success of checkpoint inhibitor therapy in the advanced setting in Merkel cell carcinoma (MCC), there is interest in exploring immunotherapy as a neoadjuvant approach, which additionally allows a window of opportunity to assess the efficacy of new immunotherapy combinations. **Methods:** We conducted a single center, phase II open label trial (NCT04869137) in patients (pts) with resectable stage II-IV MCC. All pts were to receive six weeks of neoadjuvant therapy with pembrolizumab 200mg IV q3 weeks plus lenvatinib 20mg PO daily before planned surgery ± adjuvant radiation therapy. Following local therapy, pts were to receive continued adjuvant pembrolizumab monotherapy to complete 1 year total of systemic therapy. Target accrual was 26 pts. Pathological complete response (pCR) rate was the primary endpoint of the study, with ≥15 pCR needed for the combination therapy to be considered as promising compared to a historical benchmark of ~40% pCR for single-agent anti-PD1. **Results:** Twenty-six pts were enrolled between 06/2021 and 09/2024, including 5 (19.2%) with clinical stage II disease, 20 (76.9%) with stage III, and 1 (3.8%) with stage IV. Pts were predominantly male (77%) and with a median age of 69 (range 53-88). Following neoadjuvant treatment, 2 pts (7.7%) were unable to undergo planned surgery, one due to progressive disease (PD) and one due to toxicity. Two pts who achieved a clinical response to neoadjuvant therapy declined surgery and underwent post-neoadjuvant therapy biopsies for pathological assessment. On intention to treat, 15 of the 26 pts (57.7%) achieved a pCR. With a median follow-up of 20 months, 6 pts (23.1%) have experienced disease progression, 2 during neoadjuvant therapy, 2 during and 2 after adjuvant treatment. Among pts with pathological assessment of response, pCR was associated with a lower risk of relapse, though this result was not statistically significant (13.3% vs. 33.3%, p = 0.33). Thirteen of 15 pts who achieved pCR following surgery omitted adjuvant radiation therapy and there have been no local recurrences in pCR cases. Thirteen pts (50%) experienced at least one G3 treatment related adverse event (TRAE), most commonly G3 hypertension in 10 pts (40%) that improved with dose interruption and/or dose reduction of lenvatinib. No G4-5 TRAEs were observed. At the time of analysis, one pt (neoadjuvant PD) has died from progressive MCC. Two pts have died from other causes without evidence of recurrence at last follow-up. **Conclusions:** Lenvatinib plus pembrolizumab demonstrated encouraging efficacy with anticipated toxicity when used as neoadjuvant therapy for Merkel cell carcinoma. The primary endpoint of the study was met with 57.7% of patients achieving a pathological complete response. Pts with a pCR had a lower risk of recurrence vs those without, but recurrences were seen even after pCR. Ongoing correlative studies may help to identify biomarkers for response. Clinical trial information: NCT04869137. Research Sponsor: Merck Sharp & Dohme LLC.

9515 Rapid Oral Abstract Session

Lifileucel in patients with advanced melanoma: 5-year outcomes of the C-144-01 study.

Theresa Medina, Jason Alan Chesney, Harriet M. Kluger, Omid Hamid, Eric D. Whitman, Mike Cusnir, Sajeve Samuel Thomas, Martin Wermke, Evidio Domingo-Musibay, Giao Q. Phan, John M. Kirkwood, James Larkin, Jeffrey S. Weber, Friedrich Graf Finckenstein, Jeffrey Chou, Brian Gastman, Giri Sulur, Renee Xiao Wu, Rana Fiaz, Amod Sarnaik; University of Colorado Comprehensive Cancer Center, Aurora, CO; Brown Cancer Center, Louisville, KY; Yale Cancer Center, New Haven, CT; The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA; Atlantic Health System, Morristown, NJ; Mount Sinai Medical Center, Miami Beach, FL; Orlando Health Cancer Institute, Orlando, FL; University Hospital Dresden, Dresden, Germany; Allina Healthcare Institute, Minneapolis, MN; UConn Health/Neag Cancer Center, Farmington, CT; UPMC Hillman Cancer Center, Pittsburgh, PA; Royal Marsden Hospital, London, United Kingdom; Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY; Iovance Biotherapeutics, San Carlos, CA; Iovance Biotherapeutics, Inc., San Carlos, CA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Lifileucel is a personalized, one-time tumor-derived autologous T-cell immunotherapy approved for the treatment of adult patients (pts) with advanced (unresectable or metastatic) melanoma previously treated with a programmed cell death-1 (PD-1)–blocking antibody, and, if *BRAF* V600 mutation–positive, a BRAF inhibitor with or without a MEK inhibitor. In the registrational C-144-01 study (NCT02360579), pts with advanced melanoma who received lifileucel had an objective response rate (ORR) of 31.4%. Follow-up in therapeutic trials targeting refractory patients with refractory melanoma typically span months rather than years due to lack of activity. Reflective of the durability of lifileucel, we nowreport 5-year survival outcomes from the C-144-01 study. **Methods:** C-144-01 (NCT02360579) is a phase 2, multicenter, multicohort, open-label study of lifileucel. Eligible pts had advanced melanoma that had progressed on or after immune checkpoint inhibitor and targeted therapy, where appropriate. Before lifileucel infusion, pts underwent nonmyeloablative lymphodepletion (NMA-LD; cyclophosphamide, 60 mg/kg $\times$ 2 d plus fludarabine 25 mg/m^2 $\times$ 5 d). Pts received cryopreserved lifileucel followed by up to 6 doses of interleukin-2 (IL-2; 600,000 IU/kg every 8–12 hours). The primary endpoint was ORR assessed by an independent review committee (IRC) using RECIST v1.1. Key secondary endpoints were duration of response (DOR), overall survival (OS), and safety. **Results:** Among pts who received lifileucel (n = 153; median age, 56 y; range, 20–79), 54% were male. All pts had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 and previously received anti–PD-1/PD-L1 therapy. Pts had a median of 3 prior lines of therapy (range, 1–9) and 55% were primary refractory to anti–PD-1/PD-L1 therapy. At a median follow-up of 57.8 mo, all pts have completed or discontinued the study, with 28 (18.3%) pts having completed the 5-year study follow-up. The ORR was 31.4% (complete response, 5.9%; partial response, 25.5%). Median DOR was 36.5 mo (95% confidence interval [CI]: 8.3–not reached), with 31.3% of responders completing the 5-year assessment with a sustained response. Median time to best response was 1.5 mo (range, 1.3–30.4). Median OS was 13.9 mo (95% CI: 10.6–17.8); the 5-year OS rate was 19.7% (95% CI: 13.3–27.0). Treatment-emergent adverse events were consistent with known safety profiles of NMA-LD and IL-2. The extended follow-up revealed no new safety signals. **Conclusions:** This 5-year analysis of the C-144-01 trial is the longest follow-up of the largest group of pts with melanoma treated with tumor-infiltrating lymphocytes in a single study. This study illustrates lifileucel's continued durability of response and survival benefit up to 5 years after a single administration without any long-term safety concerns. Clinical trial information: NCT02360579. Research Sponsor: Iovance Biotherapeutics Inc.

Infusion product characteristics to predict response to tumor-infiltrating lymphocyte (TIL) therapy in metastatic melanoma (MM).

Lilit Karapetyan, Kimberly Ward, Denise Kalos, Johannes Ali, Cheryl Cox, Joseph Markowitz, Andrew Scott Brohl, Zeynep Eroglu, Ahmad A. Tarhini, Nikhil I. Khushalani, Jane Messina, Kenneth Yee Tsai, John Mullinax, Jonathan S. Zager, Matthew Perez, Vernon K. Sondak, James J. Mule, Amod Sarnaik, Matthew Beatty, Shari Pilon-Thomas; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Moffitt Cancer Center - McKinley Campus, Tampa, FL; Department of Immunology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Moffitt Cancer Center & Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Moffitt Cancer Center, Tampa, FL

Background: Identification of the TIL therapy product (TILp) characteristics associated with objective response to therapy is critical to improve future adoptive TIL-based therapy. In this study we performed comprehensive phenotypic analysis of TILp in association with TIL therapeutic outcomes in consecutive patients with MM. **Methods:** Data were extracted from early-phase clinical trials of MM patients treated with TIL only, TIL plus ipilimumab, TIL plus nivolumab, and TIL plus vemurafenib at Moffitt Cancer Center. The immunophenotypic features of TILp were evaluated by flow cytometry using antibodies against checkpoints, costimulatory molecules, T cell subsets and TCRβ sequencing. Tumor reactivity was measured using HLA-matched cell lines. The relationship between TILp characteristics and both objective response and progression-free survival (PFS) was assessed in treated patients. **Results:** A total of 50 patients, 21 female (42%) and 29 male (58%), median age 49 [IQR 40–55] received lymphodepleting chemotherapy followed by TIL and interleukin-2 (IL-2). Median numbers [IQR] of infused TIL and IL-2 dose were $59e^9$ [$42\text{-}84e^9$] and 5 [4–6], respectively. Patients with objective response had a significantly higher total number of infused TIL, total number of infused $CD8^+$ TIL, and proportion of $CD8^+$ cells in the infusion product ($p < 0.05$), with high $CD8^+$ TIL being associated with improved PFS ($p = 0.0001$). The total number and proportion of infused stem cell-like memory $CD8^+$T cells ($T_{SCM,}$ $CD8^+CD45RA^+CCR7^+CD62L^+CD95^+$) were significantly higher in responders and associated with improved PFS ($p < 0.01$). TILs from responders had distinct patterns of co-inhibitory and co-stimulatory receptors' expression and were characterized by significantly higher proportion of $LAG3^+$ and $LAG3^+TIGIT^+$ co-expressed TIL of total $CD3^+$ TIL ($p < 0.05$). Proportions of $LAG3^+CD8^+$ and $TIGIT^+CD8^+$ cells were also increased in responders ($p < 0.05$) with no significant differences observed in $PD1^+CD8^+$, $BTLA^+CD8^+$, and $TIM3^+CD8^+$ cells. There was an increased proportion of $OX40^+CD8^+$ and $OX40^+4\text{-}1BB^{neg}CD8^+$ cells among responders ($p < 0.01$). T cell clonal analysis using top 20 clones revealed high persistence in responders ($p < 0.01$) measured by TCRβ overlap between ACTP and post-treatment peripheral blood. There were no significant differences in clonality, diversity and evenness in responders *vs.* non-responders. Using HLA-matched cell lines there was a trend towards HLA-matched reactive TIL and improved PFS ($p = 0.058$). **Conclusions:** Response to TIL therapy is associated with TIL persistence and distinct TILp immunophenotypic features characterized by enhanced proportion of $CD8^+$ TIL, T_{SCM} $CD8^+$ cells, and high surface expression of $LAG3^+TIGIT^+$ and $OX40^+$. Novel strategies to modulate *ex vivo* TIL expansion toward this optimal TIL phenotype may result in increased response for future trial design. Research Sponsor: None.

9517 Rapid Oral Abstract Session

OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy with regulatable membrane-bound IL15 (mbIL15) in patients (pts) with immune checkpoint inhibitor (ICI)–resistant advanced melanoma: Phase 1 results of the Agni-01 multicenter study.

Jason Alan Chesney, Gino Kim In, Alexander Noor Shoushtari, Justin Tyler Moyers, Yazan Samhouri, Tirrell T. Johnson, Rodabe Navroze Amaria, Giridharan Ramsingh, Camille Renard, Raina Duan, Lauren McLaughlin, Allison Betof Warner; UofL Health – Brown Cancer Center, University of Louisville, Louisville, KY; Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Memorial Sloan Kettering Cancer Center, New York, NY; The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA; Allegheny Health Network Cancer Institute, Pittsburgh, PA; Orlando Health Cancer Institute, Orlando, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; Obsidian Therapeutics, Cambridge, MA; Stanford University School of Medicine, Stanford, CA

Background: OBX-115 TIL are engineered to express mbIL15 regulated by the FDA-approved small-molecule drug acetazolamide (ACZ), abrogating the need for toxic high-dose IL2 after TIL infusion. Single-center phase 1 data (NCT05470283) demonstrated differentiated early safety (Amaria ASCO 2024). We report the first data evaluating OBX-115 in pts with advanced melanoma in the multicenter phase 1/2 Agni-01 study (NCT06060613). **Methods:** This single-arm, open-label study assesses safety, tolerability, and efficacy of the OBX-115 TIL cell therapy regimen in pts with advanced melanoma and NSCLC (Shoushtari AACR 2025). Phase 1 characterizes safety (treatment-emergent adverse events [TEAEs]: AEs ≤30 d after OBX-115 infusion) and tolerability in escalating dose levels of OBX-115 and ACZ to establish a recommended phase 2 dose (RP2D). Phase 2 evaluates efficacy of the regimen at RP2D (RECIST v1.1 per investigator). OBX-115 is manufactured from pt tumor tissue (core needle biopsy or surgical excision) and infused after standard- or low-dose (Cy 750 mg/m^2/d × 3; Flu 30 mg/m^2/d × 4) lymphodepletion (LD). No IL2 is administered. Oral ACZ starts day of OBX-115 infusion (QD up to 14 d), and is redosed (QD up to 7 d) every 6 wks after recovery from LD. **Results:** In phase 1,as of 01 Jan 2025, OBX-115 was successfully manufactured and infused for 11 pts with ICI-resistant advanced melanoma (median study follow-up, 22.3 wks [range, 13.3–52.1]) including 6 treated at RP2D (OBX-115 1–100×10^9 cells, ACZ 500 mg/d). Majority (n = 10) received low-dose LD, including 1 in the outpatient setting. There was no dose-limiting toxicity (DLT), treatment-emergent ICU transfer, or treatment-related mortality (TRM). Eight pts had G≥3 nonhematologic TEAEs (events in > 1 pt: hyponatremia, hypokalemia [n = 2 each]). One pt reported 2 OBX-115–related serious AEs, including 1 CRS event (G2) without IL6 elevation (IL6 < 100 pg/mL). Across dose levels (n = 11), confirmed ORR was 36% (4 PR, 5 SD; DCR 82%). For 6 pts receiving RP2D, ORR was 67% (4 PR, 2 SD; DCR 100%). **Conclusions:** Early data support clinical benefit (RP2D ORR 67%, DCR 100%) of OBX-115regulatableengineeredTIL cell therapy in the absence of IL2, including with outpatient low-dose LD. The safety profile is highly differentiated, without TRM, ICU transfer, or high-grade CRS. ACZ redosing is well-tolerated and offers an opportunity to deepen responses by inducing re-expression of mbIL15 on engrafted OBX-115 TIL, a unique capability among adoptive cell therapies. These attributes may comprehensively address the unmet need in post-ICI advanced melanoma and other cancers, and data support continued investigation of OBX-115 in the ongoing phase 2 portion of the Agni-01 study. Clinical trial information: NCT06060613. Research Sponsor: Obsidian Therapeutics.

Neutralizing antibodies and lymphocyte count as biomarkers in patients receiving oncolytic adenovirus TILT-123 and adoptive cell transfer of tumor-infiltrating lymphocytes for metastatic melanoma refractory to immune checkpoint inhibitors.

Lyna Haybout, James Clubb, Tine Monberg, Santeri Pakola, Benedetta Albieri, Susanna Juteau, Eva Ellebaek, Marco Donia, Victor Arias, Tatiana Kudling, Amir Khammari, Claudia Kistler, Suvi Sorsa, Elise Jirovec, Dafne Carolina Alves Quixabeira, Joao Manuel Santos, Victor Cervera, Brigitte Dreno, Inge Marie Svane, Akseli Hemminki; TILT Biotherapeutics Ltd., Helsinki, Finland; Cancer Gene Therapy Group, Helsinki, Finland; National Center for Cancer Immune Therapy, Department of Oncology, Copenhagen University Hospital, Herlev, Denmark; Cancer Gene Therapy Group, Translational Immunology Research Program, University of Helsinki, Helsinki, Finland; Department of Pathology, Helsinki University Hospital, Helsinki, Finland; National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology, Copenhagen University Hospital Herlev, Herlev, Denmark; National Center for Cancer Immune Therapy (CCIT-DK), Copenhagen University Hospital, Herlev, Denmark; Oncodermatology Department, Nantes University Hospital, Nantes, France; University of Nantes, CHU Nantes, Inserm, Nantes, France; National Center for Cancer Immune Therapy, CCIT-DK, Copenhagen University Hospital, Herlev, Denmark

Background: Metastatic melanoma refractory to immune checkpoint inhibitors (ICI) remains a significant challenge. Adoptive Cell Transfer of Tumor-Infiltrating Lymphocytes (ACT-TILs) shows promise but can cause adverse events. Oncolytic adenovirus TILT-123 (igrelimogene litadenorepvec) coding for TNF and IL2 combined with ACT-TILs, offers an approach without conditioning therapies. We report long-term survival data from a phase I trial (TUNINTIL NCT04217473), and correlative clinical, histologic, and immunologic biomarker analyses. **Methods:** The aim was to evaluate safety of TILT-123 and ACT-TILs in patients with metastatic melanoma refractory to ICIs. Treatment was deemed safe and feasible. TILT-123 was given intravenously (IV) and intratumorally, ACT-TILs were given IV, without preconditioning chemotherapy or post-conditioning IL2. Five cohorts were completed in a 3+3 dose-incremental design without dose-limiting toxicities. Tumor biopsies were analyzed for adenoviral (Ad) genomes, PD-L1 expression and presence of CD4+ regulatory (reg), CD4+ and CD8+ T cells by multiplex immunofluorescence (mIF). TILT-123 DNA was quantified in tumors by qPCR, anti-Ad neutralizing antibodies (nAbs) analyzed in serum using luminescence titering assay. Disease control rate (DCR) was defined as Stable Disease or better using RECIST1.1, iRECIST, and PET criteria. Association of factors with survival and DCR was determined using Spearman's rank correlation and multivariate analysis. **Results:** Patients varied in melanoma subtype (cutaneous n=8, mucosal n=5, uveal n=4), with a median age of 67 years (25-75 years). Following TILT-123 monotherapy, the DCR on D36 was 35% by RECIST 1.1 and iRECIST, and 63% by PET criteria. PET responses were seen in 31% of patients by D36. In the combination phase (D78) DCR per RECIST 1.1 or iRECIST was 38%, and 47% by PET criteria. Responses were seen in 27% of patients on D78 in PET, including a partial response lasting >8 months and a durable complete response in a mucosal melanoma patient. Median overall survival (mOS) was 447 days. Virus DNA was detected post-treatment in both injected and uninjected tumors. Patients with elevated titers of nAbs (by D22) showed a decrease in metabolism in non-injected lesions by day 36 (p=0.0101). Blood lymphocyte count decrease after TILT administration was associated with better DCR (p= 0.0188). mIF data showed patients achieving disease control had a higher percentage of intratumoral CD8+ T cells (p=0.037). **Conclusions:** ICI refractory melanoma patients receiving TILT-123 and ACT-TILs without preconditioning show signs of CD8+ T cell trafficking to the tumor microenvironment. nAbs and lymphocyte count decrease can be further investigated as biomarkers. Clinical trial information: NCT04217473. Research Sponsor: TILT Biotherapeutics Oy; Jane and Aatos Erkko Foundation; HUCH Research Funds (VTR); Cancer Foundation Finland; Sigrid Juselius Foundation; Finnish Red Cross Blood Service; EU Horizon grants; 190121193; EU Horizon grants; 811693; Albert Ehrnrooth; Karl Fazer.

9519 Poster Session

OBX-115 engineered tumor-infiltrating lymphocytes (TIL) with regulatable membrane-bound IL15 (mbIL15): Translational data from a single-center phase 1 trial in patients (pts) with immune checkpoint inhibitor (ICI)–resistant advanced melanoma.

Rodabe Navroze Amaria, Adi Diab, Hussein A. Tawbi, Isabella Claudia Glitza, Jennifer Leigh McQuade, Michael A. Davies, Alexandra Ikeguchi, Michael K.K. Wong, Sapna Pradyuman Patel, Roland L Bassett Jr., Steffy Jose, Seoung-Ae Lee, Sevinj Isgandarova, Hsinyi Lu, Giridharan Ramsingh, Camille Renard, Rachel A. Burga, Bulent Arman Aksoy, Cara L. Haymaker; The University of Texas MD Anderson Cancer Center, Houston, TX; Obsidian Therapeutics, Cambridge, MA

Background: Non-engineered TIL cell therapy is approved for ICI-resistant advanced melanoma, but requires co-administration of toxic high-dose IL2. OBX-115 engineered TIL express mbIL15 under pharmacologic regulation using the FDA-approved small-molecule drug acetazolamide (ACZ), abrogating the need for IL2. We present data supporting OBX-115 mechanism of action. **Methods:** Trial design and clinical results were previously reported (Amaria ASCO 2024; NCT05470283); briefly, pts received lymphodepletion (Day [D] -7 to -1) followed by OBX-115 infusion (D0) and ≤7 days of orally administered ACZ (D2–9). Peripheral blood (PB) and tumor tissue samples were collected for longitudinal ddPCR analysis and immune profiling. **Results:** Eight pts received OBX-115 (fresh) and are included in this analysis. PB samples demonstrated ACZ-driven OBX-115 TIL expansion, reaching a median of 1697 cells/μL at D14 (approximate day of OBX-115 expansion peak); in 3 pts with ≥6 mo follow-up, OBX-115 remained detectable through 6 mo and ongoing up to 15 mo. In the immediate post-infusion phase (up to D14), PB flow cytometry indicated expansion of product-derived CD3+CD8+ cells expressing Ki67 (during ACZ exposure) and endogenous NK cells (CD3-CD56+), while CD4+ cell levels decreased (Table). Post-infusion tumor tissue demonstrated presence of IL15-expressing T cells (of CD3+: D21, 68.6%; D42, 88.4%). Importantly, median post-infusion serum levels of IL15 and IL7 were not significantly elevated above Baseline through D42 (paired one-tailed t-test adjusted for multiple comparisons; Table); IL6 was below limit of detection at all timepoints, even in pts with fevers. T-cell receptor (TCR) clonotypes present in the OBX-115 infusion product were enriched in post-infusion PB and tumor (Table). **Conclusions:** These data support the proposed OBX-115 mechanism of action, demonstrating ACZ-driven OBX-115 TIL expansion, engraftment, and persistence; endogenous NK cell expansion, presumably driven by transactivation via mbIL15 on OBX-115, without systemic cytokine elevation; and TCR repertoire remodeling with tumor-derived, antigen-specific T cells. Investigation of OBX-115 TIL cell therapy in pts with advanced solid tumors (NCT06060613) is ongoing. Clinical trial information: NCT05470283. Research Sponsor: Obsidian Therapeutics, Inc.

Pre- and post-infusion immune profile.

Characteristic, median (N=8)	Baseline*	D14	D28	D42
CD3-CD56+ (of live, PB),† %	14.7	27.0	35.5	56.7
CD3+ (of live, PB),† %	50.7	69.9	49.5	54.2
CD8+ (of CD3+, PB),† %	27.9	75.2	85.6	87.6
CD4+ (of CD3+, PB),† %	59.7	5.7	10.6	9.3
Ki67+ (of CD8+, PB),† %	1.5	11.1	3.7	3.2
IL15, serum, pg/mL	8.5	9.5	10.0	10.8
IL7, serum, pg/mL	2.4	3.3	3.3	2.8
OBX-115 TCR clonotypes in PB, %	14.5	80.9	69.3	59.6
OBX-115 TCR clonotypes in tumor, %	28.2	Not available	86.2‡	70.4

*Pre-lymphodepletion.
†n<8.
‡D21.

9520 Poster Session

Homologous recombination deficiency signature (HRDsig) in advanced cutaneous melanoma (ACM): A genomic landscape study.

Nimisha Srivastava, Dean Pavlick, Ethan Sokol, Ole Gjoerup, Julia A. Elvin, Ryon P. Graf, Gerald Li, Julia Quintanilha, Sanchit Panda, Jeffrey S. Ross, Jade Homsi; SUNY Upstate Medical University, Syracuse, NY; Foundation Medicine, Inc., Cambridge, MA; Foundation Medicine, Inc., San Diego, CA; Department of Pathology, SUNY Upstate Medical University, Syracuse, NY; State University of New York Health Science Center at Syracuse, Syracuse, NY

Background: HRDsig can aid in identifying tumors with DNA repair deficiencies, guiding PARP inhibitor (PARPi) use. It expands treatment options beyond breast cancer gene (BRCA) mutations enabling personalized therapy. Combining PARPi with targeted therapy or immunotherapy shows promise in overcoming resistance and improving outcomes for treatment-resistant ACM. **Methods:** Formalin-fixed paraffin-embedded (FFPE) primary tumors and metastatic biopsies from 9,576 ACM cases were analyzed using hybrid capture-based comprehensive genomic profiling (CGP), evaluating all classes of genomic alterations (GA). Central pathology review was conducted for all cases. Microsatellite instability-high (MSIH) status, tumor mutational burden (TMB), genomic ancestry, and mutational signatures were derived from sequencing data. HRDsig was assessed using copy number changes and genomic scars. PD-L1 expression was determined via immunohistochemistry [Dako 22C3; tumor proportion score (TPS)]. Statistical comparisons were made using Fisher's exact test with Benjamini-Hochberg correction. **Results:** Among 9,576 ACM cases, 198 (2.1%) were HRDsig positive (HRDsig+). HRDsig+ cases when compared to HRDsig negative (HRDsig-) were older (median age: 69 vs. 67 years; p=0.034), more often female (49.5% vs. 36.2%; p=0.001), and had more GA per tumor (median: 7 vs. 6; p=0.026). HRDsig+ cases were more often of African (5.6% vs. 1.2%; p<0.0001) or American ancestry (8.1% vs. 4.1%; p=0.026) and less often European (84.3% vs. 94.0%; p<0.0001). GA more common in HRDsig+ included *IGF1R* (5.1% vs. 1.3%; p=0.003), *KIT* (11.6% vs. 5.6%; p=0.004), *KRAS* (7.1% vs. 2.7%; p=0.005), *NF1* (38.4% vs. 21.4%; p<0.0001), *RAD21* (6.7% vs. 3.0%; p=0.037), and *TP53* (40.4% vs. 24.3%; p<0.0001). HRDsig- cases exhibited higher TMB (median: 13.8 vs. 6.1; p<0.0001), more frequent TMB >10 mutations/Mb (60.9% vs. 39.9%; p<0.0001), and more UV light exposure trinucleotide signatures (57.3% vs. 36.4%; p<0.0001). GA more common in HRDsig- cases included *BRAF* (including V600E) (44.6% vs. 23.2%; p<0.0001), *CDKN2A* (49.2% vs. 36.9%; p=0.003), *NRAS* (28.0% vs. 11.6%; p<0.0001), and *TERT* (74.4% vs. 29.8%; p<0.0001). In both positive and negative groups, PD-L1 low-level expression (1-49% TPS) was comparable (43.3%-39.7%), while BRCA1/2 alterations (<2.0%) and MSIH status (0.0%-0.1%) remained rare. **Conclusions:** HRDsig+ status is rare in ACM but more frequent in non-white genomic ancestries. HRDsig+ ACM cases are less likely to have BRAF GA, more likely to have KIT GA and lower TMB levels. These findings may guide the future development of clinical trials employing combination therapies and PARPi in ACM. Research Sponsor: None.

9521 Poster Session

Association of KIT mutations with risk of central nervous system (CNS) metastasis (met) in patients (pts) with mucosal melanoma (MM).

Afsaneh Amouzegar, Merve Hasanov, Ahmed Ali, Denai R. Milton, Julie Simon, Jene Samuels, Khalida M. Wani, Debora Alejandra Ledesma, Elizabeth M. Burton, Courtney Hudgens, Hussein A. Tawbi, Jeffrey E. Gershenwald, Alexander J. Lazar, Michael A. Davies; Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Melanoma Medical Oncology, The University of Texas at MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The CNS is a frequent site of distant met in pts with cutaneous melanoma (CM). Previous studies have identified clinical, pathological, and molecular risk factors for CNS met in CM pts. However, little is known about the incidence of and risk factors for CNS met in MM pts, who overall have a worse prognosis than CM pts. **Methods:** We performed an institutionally approved retrospective review of pts diagnosed with clinically localized or regionally metastatic MM at MD Anderson Cancer Center from 1/1/1988 to 12/31/2023. Pts who presented with distant met were excluded. Pt and tumor features (including clinical testing for BRAF, NRAS, and KIT mutations) and distant recurrence events (CNS met; non-CNS met) were assessed. Tumor samples from a subset of MM pts were stained and scored for expression of PTEN (Absent vs Present), PD-L1 ($<$1% vs $\geq$1%), and KIT (Above vs Below median H-score) protein by immunohistochemistry (IHC). Time-to-CNS met and Time-to-non-CNS met were computed from the date of initial MM diagnosis (dx) to date of CNS/non-CNS met. Cumulative incidence of distant met events was determined using competing risks (death); pts alive with no met at last follow-up (f/u) were censored. Group differences were evaluated by Gray's test, and associations between measures of interest were determined using proportional sub-distribution hazards regression models. **Results:** 579 MM pts with clinically localized (73%) or regionally metastatic (27%) disease were included in the analysis. At a median f/u of 34.4 months (range 0 – 525.8), 111 pts (19.2%) had developed CNS met. The cumulative incidence of CNS met at 1, 2, 3 and 5 years was 5%, 10%, 14% and 18%, respectively. For pts with CNS met, median time from MM dx to CNS met was 26.1 months (range, 2.3 – 211.0). Most pts with CNS met presented with brain met only (90%), followed by brain met and LMD (6%), and LMD only (4%). On univariate analysis, KIT mutation (Hazard Ratio [HR] 2.78; 95% Confidence interval [CI] 1.74 – 4.44), $p<0.001$), mitotic rate 5-9/mm^2 (vs. 0-4/mm^2; HR 2.22; 95% CI 1.14 – 4.34, p=0.020), and lymphovascular invasion (HR 1.63; 95% CI 1.03 – 2.56, p=0.036) were associated with increased risk of CNS met. On multivariable analysis, KIT mutation (HR 2.77; 95% CI 1.71 – 4.51, $p<0.001$) remained significantly associated with increased risk of CNS met. In contrast, KIT mutation predicted a lower risk of non-CNS met in multivariate analysis (HR 0.55; CI 0.34 – 0.87, p=0.011). Among the 87 MM pts for whom IHC was performed on tumor samples, PTEN, KIT, and PD-L1 protein expression were not associated with risk of CNS or non-CNS met. **Conclusions:** KIT mutation is significantly associated with increased risk of CNS met in patients with clinically localized or regionally met MM. These results highlight distinct CNS met risk factors, and potential surveillance strategies, for MM compared to CM pts. Research Sponsor: SPORE (NIH/NCI 5P50CA221703-05); MD Anderson Melanoma Moon Shot program; Dr. Miriam and Sheldon Adelson Medial Research Foundation (Project number FP17016).

9522 Poster Session

Serum thymidine kinase activity (TKa) as a potential biomarker in the sequential immunotherapy and targeted therapy for metastatic BRAF V600 mutated melanoma (SECOMBIT) trial.

Hildur Helgadottir, Mariaelena Capone, Claudia Piccinini, Luisa Piccin, Piotr Rutkowski, Virginia Ferraresi, Ana Maria Arance, Michele Guida, Evaristo Maiello, Helen Gogas, Pietro Quaglino, Celeste Lebbe, Francesco Spagnolo, Maria Grazia Vitale, Ignacio Melero, Mattias Bergqvist, Diana Giannarelli, Reinhard Dummer, Giuseppe Palmieri, Paolo Antonio Ascierto; Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden; Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, Instituto Nazionale Tumori – IRCCS - Fondazione Pascale, Naples, Italy; IRST/IRCCS "Dino Amadori", Medola (FC), Italy; Veneto Institute of Oncology IOV, IRCCS, Padua, Italy; Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Sarcomas and Rare Tumors Departmental Unit - IRCCS Regina Elena National Cancer Institute, Roma, Italy; Department of Medical Oncology, Hospital Clinic Barcelona and IDIBAPS, Barcelona, Spain; Rare Tumors and Melanoma Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy; Oncology Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; First Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece; Department of Medical Sciences, Dermatologic Clinic, University of Turin, Turin, Italy; Université de Paris, AP-HP Hôpital Saint-Louis, Dermatology Department, Paris, France; Department of Medical Oncology, IRCCS Ospedale Policlinico San Martino, Genova, Italy; Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione "G.Pascale", Naples, Italy; Clínica Universidad de Navarra, Pamplona, Pamplona, Spain; Biovica International AB, Uppsala, Sweden; Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; Skin Cancer Center, University Hospital of Zurich, Zurich, Switzerland; University of Sassari, Sassari, SS, Italy; Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, Instituto Nazionale Tumori – IRCCS - Fondazione G. Pascale, Naples, Italy

Background: In melanoma, there is a need for biomarkers for predicting treatment efficacy. Thymidine kinase 1 (TK) is a cytosolic enzyme that plays a pivotal role in DNA synthesis and repair as it is part of the reaction chain to introduce thymidine into the DNA strand. Dividing cells release TK during mitotic exit and TK can be measured in blood as a biomarker of cell proliferation. Elevated levels of TK enzyme activity (TKa) have been detected in blood samples from patients with several tumor types and correlated with disease stage, prognosis, and treatment efficacy. This study is the first to evaluate the role of TKa as a biomarker in a prospective clinical trial in patients with metastatic melanoma, the SECOMBIT study (NCT02631447). **Methods:** SECOMBIT was a randomized, three-arm, phase II trial where melanoma patients received, in ARM A: BRAF+MEK inhibitors (encorafenib (E) + binimetinib (B)) and at progressive disease (PD), immune checkpoint inhibitors (ICI) (ipimumab (I) + nivolumab (N), in ARM B: I+N and at PD E+B, and in ARM C: 8-week induction of E+B before a planned switch to I+N, and at PD E+B. Serum TKa was analyzed as DiviTum Unit of Activity (DuA) by the FDA cleared and CE-labelled assay (Biovica). **Results:** Baseline serum TKa was available from 81 (38.8%) of the patients in SECOMBIT, 25, 27 and 29 in ARM A, B and C, respectively. Patients were divided into TKa-HIGH (n=41) and TKa-LOW (n=40) by the median TKa value 110 DuA (range 39-2343, IQR 74-183). The median total progression-free survival (tPFS) was 17 months (95% CI 12 to 22), and the median overall survival (OS) was 19 months (95% CI: 12 to 26) in TKa-HIGH, while the median tPFS and OS were not reached at 76 months in the TKa-LOW group (tPFS: p=0.004 and OS: p<0.001). In ARM A and B, TKa-HIGH patients had significantly worse tPFS and OS while the survival difference between TKa-HIGH and TKa-LOW was not statistically significant in ARM C (Table 1). TKa predicts prognosis independently of LDH in multivariate analysis. **Conclusions:** Baseline serum TKa levels efficiently predicted the outcome of patients with BRAF V600 mutated metastatic melanoma treated with different sequences of ICI and BRAF+MEK inhibitors. Patients with elevated TKa is an evident poor prognosis group and appears to benefit from the regime received in ARM C, with an 8-week induction of BRAF-MEK inhibitors, before ICI (sandwich approach). TKa merits further study as a potential biomarker in metastatic melanoma. Clinical trial information: NCT02631447. Research Sponsor: None.

Survival according to study arm and TKa level.

	ARM A	ARM B	ARM C
tPFS at 5 years, (rate, 95% CI)			
TKa-HIGH	10.0 (0-28.6)	38.5 (12.0-65.0)	47.1 (23.4-70.8)
TKa-LOW	52.5 (26.8-78.2)	78.6 (57.0-100)	44.4 (4.6-84.2)
P value	0.010	0.019	0.51
OS, at 5 years, (rate, 95% CI)			
TKa-HIGH	20.0 (0-44.7)	38.5 (12.0-65.0)	46.3 (22.2-70.4)
TKa-LOW	60.0 (35.3-84.7)	78.6 (57.0-100)	75.0 (50.0-99.5)
P value	0.030	0.015	0.11

9523 Poster Session

Circulating tumor DNA (ctDNA) dynamics during anti-PD-1 based therapy to predict clinical outcomes in advanced stage melanoma: A multicenter retrospective study.

Caroline Burkey, Fauzia Hollnagel, Janmesh D. Patel, Alyssa Steimle, Matthew C. Mannino, Jennifer L. Schehr, Shuang Zhao, Joshua Michael Lang, Alexander Birbrair, Adrienne I. Victor, Alice Yao Zhou, Vincent The-Luc Ma; University of Wisconsin Hospitals and Clinics, Madison, WI; University of Wisconsin Madison, Madison, WI; University of Wisconsin School of Medicine & Public Health, Madison, WI; University of Wisconsin Hospitals and Clinics, WI; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Wisconsin, Madison, WI; University of Rochester, Rochester, NY; Washington University in St. Louis, St. Louis, MO; Division of Hematology, Medical Oncology, and Palliative Care, Department of Medicine, University of Wisconsin, Madison, WI

Background: ctDNA has shown promise as a prognostic biomarker for disease relapse in resected tumors. The significance of ctDNA changes in the advanced or metastatic disease setting for predicting treatment response and survival characteristics is still under investigation. In our study, we evaluated the association between early ctDNA changes after anti-PD-1 based therapy initiation and clinical outcomes in patients with advanced stage melanoma. **Methods:** We performed a multicenter, retrospective analysis using a personalized, tumor-informed ctDNA assay (Natera) on prospectively collected plasma samples from patients with unresectable stage III/IV melanoma treated with anti-PD-1 based therapy. Baseline ctDNA levels were assessed prior to the start of treatment and at 6-8 weeks. Patients were divided into 3 cohorts based on ctDNA changes: ctDNA clearance (6-8 week level undetectable or 0 MTM/mL), ctDNA decrease (6-8 week level decreased from baseline but detectable), or ctDNA increase (6-8 week level increased from baseline). Logistic regression models were used to evaluate the odds of disease control based on the change in ctDNA levels between both time points. Cox proportional hazard models were used to study the effects of ctDNA changes on progression-free survival (PFS) and overall survival (OS). **Results:** We identified 95 patients with unresectable stage III (18%; n=17) or stage IV (82%; n=78) melanoma with cutaneous (72%; n=68), uveal (12%; n=11), mucosal (8%; n=8), or unknown (8%; n=8) primaries who were treated with dual anti-PD-1/anti-CTLA-4 (60%; n=57), dual anti-PD-1/anti-LAG-3 (17%; n=16), or anti-PD-1 monotherapy (23%; n=22). At baseline, median age was 75, median baseline ctDNA was 363 mTM/ml, and median follow up was 13.1 months; 29% (n=28) had liver metastases, 26% (n=25) had brain metastases. Using ctDNA clearance (n=40) as reference, patients with ctDNA decrease (n=23) had lower odds of disease control (OR=0.09, 95% CI 0.01-0.85, p=0.035), and shorter PFS (HR=5.15, 2.25-11.79, $p<0.001$), and OS (HR=5.72, 1.52-21.56, p=0.010); patients with ctDNA increase (n=32) had even lower odds of disease control (OR=0.01, 0.00-0.09, $p<0.001$) and even shorter PFS (HR=5.67, CI 2.62-12.24, $p<0.001$) and OS (HR=8.76, CI 2.55-30.11, p=0.001). 12-month PFS for ctDNA clearance, ctDNA decrease, and ctDNA increase were 94.3%, 63.0%, and 48.2%, respectively. 12-month OS for ctDNA clearance, ctDNA decrease, and ctDNA increase were 95.4%, 64.6%, and 50.5% respectively. **Conclusions:** ctDNA dynamics after 6-8 weeks of anti-PD-1 therapy in patients with advanced stage melanoma may be predictive of disease control, progression-free survival, and overall survival. ctDNA clearance is associated with favorable clinical outcomes. Larger studies are needed to validate the role of ctDNA as an early response biomarker in advanced disease. Research Sponsor: NIH National Center for Advancing Translational Sciences (NCATS); UL1TR002373.

9524 Poster Session

Application of a novel multiplex imaging-based immunotherapy panel and AI-powered analysis solution for predictive spatial biomarker identification on immunotherapy-treated melanoma patients.

Paolo Antonio Ascierto, Marion Bonnet, Pedro Machado Almeida, Gabriele Madonna, Maria Giuseppina Procopio, Luisa Piccin, Claudia Piccinini, Piotr Rutkowski, Virginia Ferraresi, Ana Maria Arance, Michele Guida, Helen Gogas, Ignacio Melero, Reinhard Dummer, Giuseppe Palmieri, Saska Brajkovic, Michael Mints, Shai Bookstein, Ettai Markovits, Antonio Sorrentino; Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, Instituto Nazionale Tumori – IRCCS - Fondazione G. Pascale, Naples, Italy; Lunaphore Technologies, Tolochenaz, Switzerland; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Veneto Institute of Oncology IOV, IRCCS, Padua, Italy; IRST/IRCCS “Dino Amadori”, Medola (FC), Italy; Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Sarcomas and Rare Tumors Departmental Unit - IRCCS Regina Elena National Cancer Institute, Roma, Italy; Medical Oncology, Hospital Clinic Barcelona and IDIBAPS, Barcelona, Spain; Rare Tumors and Melanoma Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy; First Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece; Center for Applied Medical Research (CIMA), University of Navarra, Navarra Institute for Health Research (IdISNA), Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Pamplona, Spain; Skin Cancer Center, University Hospital of Zurich, Zurich, Switzerland; University of Sassari, Sassari, SS, Italy; Nucleai, Chicago, IL; Nucleai, Tel Aviv, Israel

Background: There is an urgent need for more robust methods to differentiate immunotherapy responders from non-responders. In this study, we present a novel multiplex imaging (MI)-based immunotherapy panel and a comprehensive analysis pipeline to characterize the spatial distribution and function of immune cells and its application for spatial biomarker detection in a cohort of immunotherapy-treated melanoma patients. **Methods:** We designed a 28-plex panel to perform sequential immunofluorescence (seqIF) on the COMET platform to target key biomarkers associated with tumor microenvironment (TME), immune cell infiltration, and immune checkpoint pathways. Pre-treatment biopsies were obtained from 12 patients with known long-term response or rapid progression to immunotherapy combination treatment from the SECOMBIT Trial (NCT02631447) and profiled utilizing Nucleai’s deep-learning-based MI analysis pipeline, aiming to identify spatial biomarkers that can differentiate between long-term responders and non-responders. We identified 15 cell types, including 10 immune cell populations, in addition to 10 cell state markers. Cells were assigned to the tumor area or TME, and spatial features were calculated based on cell type, marker positivity, and gross area assignment. **Results:** Our novel MI panel and analysis pipeline demonstrated highly balanced accuracy (> 0.8) and F1 scores (> 0.8) in cell typing and protein quantification for most cell types and markers. This analysis pipeline enabled the quantification of known biomarkers such as T cell activation states, T cell infiltration patterns, and tertiary-lymphoid structure maturation. A comparison of calculated spatial features between long-term responders and rapid progressors revealed distinct immune cell interactions and differences in activation status across the tumor areas associated with response. Within the tumor area, the reciprocal interactions of tumor cells, cytotoxic CD8 T-cells and antigen-presenting cells (APC) were associated with a better outcome. In contrast, a high percentage of proliferating regulatory T cells within the tumor invasive margin was associated with a worse outcome. In the adjacent TME, endothelial cell interactions with T-cells and macrophage proliferation were associated with immunotherapy resistance. In contrast, the interaction between HLA-DR-expressing macrophages and APC cells was associated with an improved clinical outcome. **Conclusions:** Integrating MI with AI analysis has the potential to enhance our understanding of treatment efficacy and resistance mechanisms. Our preliminary data demonstrate that area-specific immune niches contribute to the success or failure of immunotherapy response and highlight the importance of spatial biology in predicting immunotherapy outcomes. Clinical trial information: NCT02631447. Research Sponsor: Lunaphore.

RELATIVITY-020: Intracranial (IC) activity of nivolumab + relatlimab (NIVO + RELA) in patients (pts) with PD-(L)1 refractory melanoma with melanoma brain metastases (MBM).

Hussein A. Tawbi, F. Stephen Hodi, Evan J. Lipson, Eva Muñoz Couselo, James Larkin, Caroline Gaudy-Marqueste, Luke Mantle, Mark Semaan, Julius Strauss, Ruiyun Jiang, Diederik J. Grootendorst, Divya Patel, Paolo Antonio Ascierto; The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Royal Marsden Hospital, London, United Kingdom; Aix-Marseille University, CHU Timone, Marseille, France; University of Colorado Cancer Center, Aurora, CO; Bristol Myers Squibb, Princeton, NJ; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy

Background: NIVO + RELA is an anti-PD-1 + anti-LAG3 combination approved for the treatment of pts with advanced melanoma, but data on activity in pts with MBM are lacking. NIVO + RELA prolonged time to and decreased incidence of development of new brain lesions vs NIVO in RELATIVITY-047 (Tawbi, 2024 ASCO). Preliminary BLUEBONNET data (n = 9) showed a NIVO + RELA IC overall response rate (ORR) of 44% (Phillips, 2024 SNO/ASCO). This post hoc analysis investigated IC activity in pts with PD-(L)1–refractory melanoma treated with NIVO + RELA in the phase I/IIa RELATIVITY-020 trial (NCT01968109). **Methods:** Pts with anti-PD-(L)1–refractory melanoma treated with NIVO + RELA in RELATIVITY-020 parts C, D, or E with possible IC lesions were included. Brain imaging from these pts (eg, those with stable MBM at baseline) were interpreted by blinded independent central review (BICR) using modified RECIST v1.1 specific to the CNS. Efficacy endpoints for BICR-confirmed pts included confirmed IC response, target IC lesion reduction, and time to IC progression. **Results:** BICR analysis confirmed 27 pts had ≥ 1 MBM; of these, 59% had an ECOG PS 0, 30% had a *BRAF* mutation, and 48% had liver lesions. Pts had a median (range) of 2 (1–10) prior therapies, including anti-PD-(L)1 (100%), anti-CTLA-4 (63%, including 44% NIVO + ipilimumab), BRAF/MEKi (26%), and brain radiotherapy (81%, with 26% receiving the radiotherapy < 3 mo prior to first dose). With a minimum follow-up of 54.4 mo, confirmed IC ORR was 22% and clinical benefit rate (CBR) was 63% (table). Median duration of IC response was not reached. Target IC lesions were identified in 17 pts; 14 had both a baseline lesion and ≥ 1 on-treatment brain scan. Median best reduction from baseline for those 14 pts was 19.5%; 6 pts had a reduction ≥ 30%. Median time to IC progression (as first progression) was not reached, with 63% of pts event free for > 3 y (events/N = 7/27). Median overall survival was 21.5 mo (95% CI, 10.9–29.4) with rates of 70% at 1 y and 27% at 3 y (events/N = 22/27). **Conclusions:** A previous Part D report of this study showed a heavily pre-treated anti-PD-(L)1 refractory melanoma pt population with 12% ORR in response to NIVO + RELA irrespective of tumor location; here a subpopulation of similar pts with IC lesions compared favorably: 22% ORR and 63% CBR per CNS-specific modified RECIST v1.1. Prospective and larger studies are needed to confirm these findings. Clinical trial information: NCT01968109. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (N = 27)
Confirmed IC ORR,[a] n (%)	6 (22)
(95% CI)	(9–42)
CR, n (%)	1 (4)
PR, n (%)	5 (19)
SD, n (%)	11 (41)
PD, n (%)	5 (19)
UTD, n (%)	5 (19)
Confirmed IC CBR,[b] n (%)	17 (63)
Median time to IC response, mo (range)	3.2 (1.7–53.4)
Median duration of IC response, mo (95% CI)	NR (4.6–NR)

[a]CR+PR; [b]CR+PR+SD; CR, complete response; IC, intracranial; NR, not reached; PD, progressive disease; PR, partial response; SD stable disease; UTD, unable to determine.

Randomized dose evaluation of nivolumab + relatlimab (NIVO + RELA) in patients (pts) with advanced melanoma: Results from RELATIVITY-020.

Georgina V. Long, Stéphane Dalle, Hussein A. Tawbi, Katriina Johanna Jalkanen, Paolo Antonio Ascierto, Reinhard Dummer, Sofie Wilgenhof, Paul Lorigan, Brigitte Dreno, Andrew Graham Hill, Evan J. Lipson, James Larkin, Uwe Marc Martens, Eva Muñoz Couselo, Julius Strauss, Diane Wolf, Sourav Mukherjee, Sonia Dolfi, Satyendra Suryawanshi, Caroline Gaudy-Marqueste; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; Dermatology, Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; The University of Texas MD Anderson Cancer Center, Houston, TX; Helsinki University Hospital, Helsinki, Finland; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Department of Dermatology Universität Zürich, Zürich, Switzerland; Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; The Christie NHS Foundation Trust, Manchester, United Kingdom; University Hospital of Nantes, Nantes, France; Tasman Oncology Research, Southport Gold Coast, QLD, Australia; Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Royal Marsden Hospital, London, United Kingdom; SLK Clinics Heilbronn GmbH, Heilbronn, Germany; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Bristol Myers Squibb, Princeton, NJ; Aix-Marseille University, CHU Timone, Marseille, France

Background: NIVO + RELA is approved at 480 mg NIVO + 160 mg RELA Q4W (480/160) dosing for treatment of advanced melanoma based on RELATIVITY-047. A higher dose of 480 mg NIVO + 480 mg RELA (480/480) is under investigation in other tumor types. Here, we report results from RELATIVITY-020 Part E, which aimed to compare efficacy and safety of first-line (1L) 480/480 vs 480/160 dosing in pts with treatment-naive advanced melanoma and evaluate 480/480 dosing in pts with advanced melanoma who progressed on prior anti–PD-1 therapy (PD-1 refractory [RF]). **Methods:** RELATIVITY-020 (NCT01968109) is a phase 1/2a, dose-escalation and cohort-expansion, open-label trial. For Part E, pts with treatment-naïve advanced melanoma were randomized 1:1 to 480/480 vs 480/160 A single-arm cohort was enrolled to evaluate 480/480 dosing in pts with PD-1 RF advanced melanoma. Primary endpoints were safety and objective response rate (ORR) per BICR using RECIST v1.1. Secondary endpoints included duration of response (DOR) and PFS. Exploratory analyses included OS and pharmacodynamics. **Results:** As of clinical cutoff (May 22, 2024, min follow-up 33 mo), ORR was higher with the 1L 480/480 vs the 480/160 dose, while median (m) DOR, mPFS, and mOS were similar across the two arms, with numerically lower mPFS and 24-mo PFS/OS rates with the 480/480 dose (Table). With the 1L 480/480 vs 480/160 doses, 34% vs 36% of pts had grade 3–4 treatment-related AEs (TRAEs), and any grade TRAEs led to treatment discontinuation (d/c) in 29% vs 19% of pts, respectively. There was 1 treatment-related death (immune-mediated lung disease) in the 1L 480/480 arm vs none in the 480/160 arm. Treatment duration was shorter with the 1L 480/480 (m 5.6 mo) vs 480/160 dose (m 8.3 mo). Higher LAG-3 occupancy was observed with 1L 480/480 vs 480/160 dosing; however, there was no difference in Th1-associated cytokine levels. For the RF 480/480 arm (Table), outcomes were similar to published Part D data for RF 480/160 dosing. **Conclusions:** Although the 480/480 dose yielded higher ORR and LAG-3 occupancy levels than the 480/160 dose, it did not translate into improved survival outcomes or differences in Th1 cytokine levels. The 1L 480/480 dose also led to a higher rate of d/c due to TRAEs than the 480/160 dose. RF 480/480 dosing yielded similar results to RF 480/160 dosing from RELATIVITY-020 Part D. Clinical trial information: NCT01968109. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA 480/480 (N = 77)	NIVO + RELA 480/160 (N = 77)	NIVO + RELA RF 480/480 (N = 95)
ORR, % (95% CI)	61.0 (49.2–72.0)	48.7 (37.0–60.4)	10.6 (5.2–18.7)
mDOR, mo (95% CI)	NR (40.3–NR	NR (32.3–NR)	NR (3.1–NR)
mPFS, mo (95% CI)	26.8 (11.1–NR)	33.3 (11.0–NR)	1.8 (1.8–3.4)
PFS rate, % (95% CI)			
12 mo	61 (49–71)	61 (49–72)	19 (12–28)
24 mo	51 (39–62)	56 (43–67)	10 (5–19)
mOS, mo (95% CI)	NR (29.0–NR)	NR (40.0–NR)	12.9 (8.2–16.6)
OS rate, % (95% CI)			
12 mo	83 (73–90)	82 (71–89)	51 (40–60)
24 mo	66 (54–75)	73 (62–82)	30 (21–40)
Grade 3/4 TRAEs, %	34	36	17
Any grade TRAE leading to d/c, %	29	19	9

NR, not reached.

Real-world comparison of survival with nivolumab (NIVO) + relatlimab (RELA) vs NIVO + ipilimumab (IPI) in advanced melanoma.

Michael A. Postow, Sekwon Jang, Jennell Palaia, Andriy Moshyk, Divya Patel, Abraham Selvan, Viviana Garcia Horton, Zheng-Yi Zhou, Yiqiao Xin, Yuehan Zhang, Matthew Mattera, Loren Ormenaj, Christopher D. Lao, Justin C. Moser; Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY; Inova Schar Cancer Institute, Fairfax, VA; Bristol Myers Squibb, Princeton, NJ; Analysis Group, New York, NY; HonorHealth Research Institute, Scottsdale, AZ

Background: An indirect-treatment (Tx)-comparison (ITC) suggested first-line (1L) NIVO + RELA may have similar efficacy vs NIVO + IPI in clinical trial patients (pts) with untreated advanced melanoma. However, there is no real-world study comparing these Tx. This study compared survival outcomes among pts with advanced melanoma treated with 1L NIVO + RELA or NIVO + IPI in the Flatiron Health EHR-derived de-identified database, which includes ≥ 280 oncology clinics across the US. **Methods:** Data were extracted for pts aged ≥ 18 yrs who received 1L NIVO + RELA or NIVO + IPI between March 18, 2022 (date of NIVO + RELA FDA approval) and March 31, 2024. Pts who received adjuvant Tx, including anti–PD-1, were included, while pts with other primary cancers or treated in any clinical trial were excluded. Endpoints were OS and real-world PFS from start of 1L Tx. Outcomes were summarized using Kaplan–Meier methods, and Tx were compared using Cox models adjusted for age, sex, practice type, BRAF, brain metastases (mets), liver mets, prior adjuvant anti–PD-1 monotherapy, time from advanced melanoma diagnosis to start of 1L Tx, ECOG PS, stage, and LDH. Missing data for ECOG PS, BRAF, stage, and LDH were imputed. **Results:** Median (m) follow-up was 7.4 mo for NIVO + RELA (N = 408) and 7.7 mo for NIVO + IPI (N = 600). The NIVO + RELA group was older (m [IQR], 74.1 [65.9–81.5] yrs) than the NIVO + IPI group (66.2 [57.3–74.5] yrs), but generally had better prognostic factors (Table). Prior anti–PD-1 adjuvant Tx was 12% in both groups, while time from end of adjuvant Tx to 1L Tx and time from advanced melanoma diagnosis to 1L Tx trended longer with NIVO + RELA vs NIVO + IPI (Table). 74% of the NIVO + RELA group and 70% of the NIVO + IPI group were missing PD-L1 status, while 16% vs 20%, respectively, had PD-L1 > 1% (P = 0.61). mOS was not reached (NR) for both groups, with 95% CIs of 20.1–NR mo for NIVO + RELA vs 21.5–NR mo for NIVO + IPI (adjusted HR, 0.91 [95% CI, 0.70–1.18]). Median rwPFS was longer with NIVO + RELA (11.5 [8.9–18.7] mo) vs NIVO + IPI (4.8 [3.7–6.3] mo; adjusted HR, 0.75 [0.61–0.91]). **Conclusions:** This real-world study supports the ITC observation that NIVO + RELA and NIVO + IPI convey similar OS benefits for pts with advanced melanoma. The longer rwPFS for NIVO + RELA vs NIVO + IPI warrants additional research with longer follow-up and further evaluation of baseline characteristics, as the NIVO + IPI group had poorer prognostic factors. Important limitations included short follow-up, covariate missingness, and potential unmeasured confounding. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (N = 408)	NIVO + IPI (N = 600)
Community practice,[a] %	62	77
Brain mets,[a] %	9	21
Liver mets,[a] %	7	11
LDH ≤ ULN,[a,b] %	76	61
***BRAF* mutant,[a,b] %**	40	50
ECOG PS,[b] %		
0–1	89	89
≥ 2	11	11
Time from advanced diagnosis to 1L Tx (mo)[a], m (IQR)	1.4 (0.8–3.0)	1.1 (0.7–2.1)
Time from end of adjuvant therapy to 1L Tx (mo), m (IQR)	13.0 (3.4–30.0)	8.3 (0.1–20.3)

[a]Between-Tx difference $P < 0.05$.
[b]Includes imputed values.

9528 Poster Session

Characteristics and predictors of chronic immune-related adverse events (irAEs) following anti-PD-1 (PD1) treatment for melanoma.

Roma A. Kankaria, Andrea Boutros, Marlies Pinzon, Reilly Fankhauser, Christian B. Agbisit, Alissa Kalyan, Aleigha Lawless, Georgina V. Long, Ryan J. Sullivan, Janice M. Mehnert, Suthee Rapisuwon, Justin M. Balko, Matteo S. Carlino, Alexander M. Menzies, Douglas Buckner Johnson; Vanderbilt University School of Medicine, Nashville, TN; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Crown Princess Mary Cancer Care Centre, Westmead, Australia; Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; Perlmutter Cancer Center, New York University Langone Health, New York, NY; Mass General Cancer Center, Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Vanderbilt-Ingrim Cancer Center, Vanderbilt University Medical Center, Nashville, TN; Crown Princess Mary Cancer Centre, Westmead, Australia; Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN

Background: Adjuvant PD1 treatment improves clinical outcomes in high-risk resected melanoma. We have shown that adjuvant PD1 can lead to irAEs that become chronic in up to 46% of treated patients (pts). We performed longer follow-up (f/u) to further characterize chronic irAEs from adjuvant PD1 treatment and assessed risk factors to determine predictors for their development. **Methods:** We retrospectively analyzed pts treated with adjuvant PD1 for resected stage III-IV melanoma from 2015-2024 from 6 institutions. All pts had at least 12 months of f/u after PD1 initiation. We collected demographics, treatment details, and outcomes. We characterized type, grade, management, duration, and resolution of acute (onset during PD1) and chronic (persisting at least 3 months after PD1 cessation) irAEs. We performed Olink 96-protein inflammation assay in plasma from pts with and without chronic non-endocrine irAEs at 12 months after PD1 initiation. **Results:** We included 304 pts; 184 (61%) were male, and median age at PD1 initiation was 64 years. Among all pts, 221 (73%) developed acute irAEs, and 147 (48%) developed chronic irAEs; 59 pts had chronic endocrine irAEs, 99 had chronic non-endocrine irAEs, and 11 had both. At last f/u (median 61.4 months), 104 (34%) pts had ongoing irAEs. The most common chronic irAEs were hypothyroidism/thyroiditis (n=45, 15%), arthritis (n=25, 8%), dermatitis (n=17, 6%), hypophysitis/adrenal insufficiency (n=16, 5%), and xerostomia (n=10, 3%). Twenty (7%) pts experienced chronic toxicities outside of classical irAEs, most often fatigue (n=14, 5%), orthostasis (n=2, 1%), and headache (n=2, 1%). We then assessed risk factors for chronic irAEs compared with acute, resolving irAEs (excluding endocrine irAEs since nearly all become chronic). We found that peak steroid dose was similar in patients with and without chronic irAEs (median 50 mg for both groups, p=0.33). Time to irAE onset was similar in patients with and without chronic irAEs (median 91 vs. 114 days, p=0.78). Time to steroids from symptom onset trended longer for those with chronic irAEs (median 7 vs. 4 days, p=0.18) but was not statistically significant. In proteomic analysis, 24/96 cytokines had higher expression (0 with lower expression) in pts with chronic irAE (n=17) compared with controls (n=10), including IL-8 (p=0.02), IL-17 (p=0.049), TNF (p=0.02), VEGFA (p=0.005), and soluble PD-L1 (p=0.03). **Conclusions:** Among this large cohort of pts with melanoma treated with adjuvant PD1, chronic irAEs were common, persistent, and associated with elevated circulating cytokines, which could suggest possible therapeutics. No obvious predictors of chronic irAEs were identified outside of organ affected; analyses are ongoing. Given the long-term survival of pts treated with adjuvant PD1, monitoring and managing chronic irAEs is crucial. Research Sponsor: None.

9529 Poster Session

Safety and efficacy analysis of DNV3 plus toripalimab and chemotherapy in advanced melanoma: An open-label investigator-initiated trial.

Jing Lin, Lizhu Chen, Zuoxiang Xiao, Yuping Lu, Ling Chen, Dingyi Wang, Ping Chen, Huishan Zhang, Wei Yan, Yu Chen; Department of Medical Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China; Zhejiang Shimai Pharmaceutical Co., Ltd., Hangzhou, China; Department of Phase I Clinical Trial Ward, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian Province, China

Background: Previous studies have shown that combining LAG-3 and PD-1 inhibitors is effective in advanced melanoma. Here, we presented the safety and efficacy of DNV3, a LAG-3 inhibitor, in combination with a PD-1 inhibitor and chemotherapy for patients with advanced acral and mucosal melanoma. **Methods:** Eligible patients were adults with confirmed unresectable or metastatic melanoma and an ECOG performance status of 0 or 1. BRAF-mutant patients must had progressed after BRAF inhibitor treatment. The dosages for chemotherapy (albumin-bound paclitaxel at 260 mg/m^2 on Day 1 and cisplatin at 25 mg/m^2 on Days 1 to 3 for the first 6 cycles) and DNV3 (administered at 3 mg/kg) were based on body surface area and weight, while Toripalimab was given at a fixed dose of 240 mg. The combination therapy was administered every 3 weeks. DNV3 and Toripalimab were continued for up to 2 years or until withdrawal from the study. The primary endpoint is the objective response rate (ORR), with secondary endpoints including progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and overall survival (OS). **Results:** Overall, 27 patients participated (13 mucosal melanoma; 6 acral melanoma; 5 cutaneous melanoma; 3 unknown primary melanoma). 77.8% patients had prior anti-PD-(L)1 therapy. At a Nab-Paclitaxel dose of 260mg/m^2, 94.4% had treatment-related adverse events (TRAEs), with 50% facing severe TRAEs like infection and bone marrow suppression, leading to one death and a dose reduction for 9 patients. At 200mg/m^2, 77.8% had TRAEs, and 22.2% had severe TRAEs, mainly decreased PLT/WBC counts and bacteremia, with no further deaths. Among the 15 patients (55.6%) who experienced immune-related adverse events (irAEs), 6 (22.2%) had grade 3 or 4 irAEs, with no reported grade 5 cases. The most common grade 3 irAE was infection. An ORR of 37.0% (95% CI: 19.4% to 57.6%) was observed in 10 patients , 6 of whom had liver metastases according to RECIST 1.1 criteria. The median DOR had not yet been reached (95% CI: 3.65 months to not evaluable). Among the 27 patients, the overall ORR was 37%, with subtypes showing 38.5% for mucosal, 80% for cutaneous, and 16.7% for acral melanomas. Expression levels of BRAF or PD-L1 did not predict ORR within these subgroups. As of the cutoff date, neither median PFS nor OS had been achieved. **Conclusions:** The study provided preliminary evidence of the tolerability and potential efficacy of the combination of DNV3 plus Toripalimab with chemotherapy in patients with advanced melanoma, particularly in those with mucosal melanoma and liver metastases. Clinical trial information: ChiCTR2400079387, ChiCTR2400079543. Research Sponsor: None.

Prognostic implications of glycemia in non-diabetic patients with metastatic melanoma undergoing immunotherapy.

Domenico Mallardo, Anita Minopoli, Maria Ingenito, Margaret Ottaviano, Lucia Festino, Lucia Di Capua, Vito Vanella, Claudia Trojaniello, Maria Grazia Vitale, Michael D. Bailey, Francesca Sparano, Bianca Arianna Facchini, Andrew M. White, Corrado Caraco, Ester Simeone, Alessandra Cesano, Alfredo Budillon, Ernesta Cavalcanti, Paolo Antonio Ascierto; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale", Naples, Italy; Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione "G.Pascale", Naples, Italy; Bruker Spatial Biology, Seattle, WA; Bruker Spatial Biology, Bremerton, WA; ESSA Pharmaceuticals, South San Francisco, CA

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the cancer therapeutic landscape, significantly improving the survival of patients (pts) with advanced malignancies. Previous studies have shown that diabetic pts have a higher risk of cancer-related mortality compared to those without diabetes. This retrospective study aimed to investigate the prognostic impact of glycemia on ICI treatment outcomes in non-diabetic metastatic melanoma pts. **Methods:** Glycemic levels were assessed at three distinct time points within a two-week period prior to the initiation of ICI therapy in 1079 non-diabetic metastatic melanoma pts treated with anti-PD1 and anti-CTLA4 either as monotherapy or in combination. Blood glucose concentrations were determined enzymatically using the cobas c-501 system (Roche, normal range 70-110 mg/dL). Interleukin-6 (IL-6) levels were assessed in 378 pts using Electrochemiluminescence Immunoassays and gene profiling analysis was performed on 95 baseline RNA using NanoString IO360 panel. Pts characteristics are listed in Table 1. Spearman's correlation was used to assess the association between variables. Survival rates were analyzed using the Kaplan-Meier method. **Results:** ROC curve analysis identified a blood glucose cut-point of 93.33 mg/dL. Pts with low glycemia had a better overall survival (median: 27.7 vs 14.5 months, HR=0.68, $p < 0.0001$) and progression free survival (median: 7.4 vs 4.3 months, HR=0.74; $p < 0.001$) compared to pts with elevated glycemia. This trend was confirmed in subgroups analysis (anti-PD1; anti-CTLA4), except for pts treated with the combination of anti-PD1 plus anti-CTLA4 as well as in line of treatment stratification (first, second and ≥3). Glycemia was found to be positively associated with elevated IL-6 levels (rho 0.16, $p<0.01$). Transcriptomic analysis showed an association between glycemia and genes related to inflammatory activity (S100A12; CD40) and cell cycle regulation (CNTFR; PTEN). Glycemia predicts prognosis independently of LDH and line of treatment in multivariate analysis. **Conclusions:** Elevated glycemia is associated with poor prognosis in pts with metastatic melanoma treated with ICIs. Biomarker analysis revealed an association between glycemia levels with pro-inflammatory cytokine IL-6 and genes linked to inflammation and cell cycle progression. Further investigations are needed in order to endorse the data and validate the glycemia cut-point. Research Sponsor: None.

Patient characteristics.

Patient characteristics	N = 1079
Median age	59 (range 19-91)
Gender: female/male, n (%)	448 (41)/631 (59)
CNS metastases at baseline, n (%)	201 (20)
BRAF Status, n (%)	
Wild type, n (%)	596 (55)
Mutation, n (%)	404 (38)
NA, n (%)	80 (7)
T2DM, n (%)	47 (4)
ORR, n (%)	261 (24)
Anti-PD1, n (%)	646 (60)
Anti-CTLA4, n (%)	272 (25)
Anti-PD1+ Anti-CTLA4, n (%)	161 (15)
First line, n (%)	623 (58)
Second line, n (%)	325 (30)
Third line ≥, n (%)	131 (12)

9531 Poster Session

Trick-MCC: Final results from the proof-of-concept investigator-initiated study of combination therapy with anti–PD-1, anti–LAG-3, and anti–TIM-3 in participants with advanced or metastatic PD-(L)1 refractory Merkel cell carcinoma (NCT06056895).

Natalie J. Miller, Grete Ambrazeviciute, Tomas J. Bencomo, Kate Biese, Wenwen Chen, Candice Church, Sumia N. Dakhil, Priscilla Kim, Samantha Kiriluk, Rima Kulikauskas, Carina D. Morningstar, Vivian Nguyen, Thomas Pulliam, Samantha E. Szumski, Joshua Veatch, Paul Nghiem, Shailender Bhatia; University of Washington, Seattle, WA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: Merkel cell carcinoma (MCC) is an aggressive and highly immunogenic skin cancer associated with the Merkel cell polyomavirus. Over 50% of patients with metastatic MCC do not derive durable benefit from PD-(L)1 therapy alone. High expression of additional immune checkpoints LAG-3 and TIM-3 on MCC-specific CD8 T cells suggested that concurrent triple checkpoint blockade may overcome immune evasion in patients with PD-(L)1 refractory MCC. **Methods:** TRICK-MCC (Triple Immune Checkpoint Inhibition in MCC) is an investigator initiated, single center, proof-of-concept clinical trial studying concurrent treatment with anti-PD-1 (retifanlimab, q4w), anti-LAG3 (tuparstobart, q2w) and anti-TIM-3 (verzistobart, q2w) in patients with advanced/metastatic MCC that progressed after PD-(L)1 therapy. After receiving standard frequency dosing for the first 24w, benefitting patients are transitioned to reduced frequency dosing at q6w for up to 2 years total or until disease progression, unacceptable toxicity, or study withdrawal. Primary endpoint is objective response rate (ORR). Secondary endpoints include duration of response, disease control rate, progression free and overall survival, and incidence and severity of adverse events (AE). Serial tumor biopsies and blood samples are obtained in all patients, unless not feasible/safe. **Results:** Twelve (out of planned 20) patients were enrolled between Nov 2023 and Jan 2025, before the study was closed to enrollment for administrative reasons by the funding sponsor. At the time of abstract submission, ORR and AE data are available for 10 patients. Two of 10 patients (20%) have partial response and one (10%) has stable disease (26% decrease in tumor size) per RECIST 1.1. Therapy has generally been well tolerated, with immune-related AEs observed in 4 (40%) patients, all Grade 1-2. One patient discontinued therapy due to an AE, grade 5 encephalopathy (anti-IgLON5 disease) diagnosed 7 mo into treatment with unclear relationship to study agents. Correlative studies of pre- and post-treatment tumor and blood specimens are ongoing to characterize the prevalence and significance of cancer-specific T cell exhaustion markers (including PD-1, LAG-3 and TIM-3), and additional mechanisms of PD-(L)1 resistance. Updated translational and clinical results will be presented at the meeting. **Conclusions:** Concurrent triple immune checkpoint blockade of PD-1, LAG-3 and TIM-3 appears to be generally well tolerated and associated with clinical activity in our cohort of patients with PD-(L)1 refractory MCC. Our data suggests TIM-3 and LAG-3 are contributing to immune evasion in a subset of patients with PD-(L)1 resistant MCC, providing support for further investigation of these pathways in larger trials. Clinical trial information: NCT06056895. Research Sponsor: Incyte Biosciences; Kuni Foundation; Jacob Green Foundation.

9532 Poster Session

Resistance to anti-PD-1 immunotherapy for stage III and IV melanoma: Results from a global multi-site chart review.

XiangLin Tan, Ryan J. Sullivan, Kavita Gandhi Morar, Alicia Delibes, Ignacio Méndez, Ruixuan Jiang, Clemens Krepler, Elizabeth Mary Gaughan, Aparna Dodla Rao, James Isaacs, Marcin Radoslaw Dzienis, Maria L. Wei, Xiaochen Zhong, Alexandra So, Miso Kim, Yu Jung Kim, Ryan Michael Weight, Nawab Qizilbash, Irene M. Shui; Merck & Co, Inc., Rahway, NJ; Massachusetts General Hospital Cancer Center, Boston, MA; OXON Epidemiology, Madrid, Spain; Merck & Co., Inc., Rahway, NJ; University of Virginia, Charlottesville, VA; Peter MacCallum Cancer Centre, Melbourne, Australia; Cleveland Clinic, Cleveland, OH; Gold Coast University Hospital, Southport, Australia; University of California San Francisco, San Francisco, CA; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; The Melanoma and Skin Cancer Institute, Denver, CO

Background: Anti-PD-1 immunotherapy has been approved for the treatment of stage III and IV melanoma. Real-world data on its resistance is needed to facilitate the development of combinatorial approaches to overcome anti-PD-1 resistance. Objectives: To estimate the percentage and understand patient/disease characteristics and survival of those receiving anti-PD1 therapy who experience primary resistance and late relapse in the adjuvant (resectable) setting, and primary, secondary resistance and late progression in the advanced (unresectable/metastatic) setting. **Methods:** A retrospective chart review was conducted in 22 sites in Australia, France, Germany, South Korea, UK and USA. Adult patients who began anti-PD-1 therapy for stage III or IV melanoma from 1 Jan 2018 until 12 months before the start of data collection were included. SITC Immunotherapy Resistance Taskforce definitions of resistance were used, and late relapse/progression defined if occurring more than 12 weeks after last dose of anti-PD-1. The percentage of patients with primary, secondary resistance or late relapse/progression were calculated. Time to death was analysed using Kaplan-Meier. Univariate tests were used to compare baseline characteristics and survival by type of resistance. **Results:** Of 981 eligible patients, 738 were included in the full analysis set. In the adjuvant setting (n=240), 53 (22.1%) patients developed primary resistance and 60 (25.0%) experienced late relapse. In the advanced setting (n=498), 222 (44.6%), 50 (10.0%) and 64 (12.9%) patients developed primary, secondary resistance, and late progression, respectively. In the adjuvant setting, a greater proportion of patients with primary resistance (66%) or late relapse (75%) were male than in those with no relapse (52%) ($p=0.007$). Asian patients experienced less late relapse (0.0%) than White patients (28.2%) but more primary resistance (61.5% vs. 18.4%) ($p<0.001$). In the advanced setting, 48.6% of Asian patients developed primary resistance, 37.8% secondary resistance, 5.4% late progression vs. 40.8%, 8.8% and 12.7% of White patients ($p<0.001$). No significant difference was observed in age, BMI, disease severity, Charlson index score and comorbid conditions by type of resistance. In both settings, time to death varied significantly by type of resistance ($p<0.001$). Patients with primary resistance had the poorest survival: a mean of 42 months in the adjuvant setting and 31 months in the advanced setting (39 months in those with secondary resistance). **Conclusions:** A large proportion of patients developed resistance or late relapse/progression and require alternative therapy after anti-PD-1, highlighting a substantial unmet medical need. A greater proportion of Asian patients developed resistance compared to White patients, possibly due to differences in melanoma subtype. Patients with primary resistance had the poorest survival. Research Sponsor: Merck & Co., Inc.

9533 Poster Session

CemiplimAb-rwlc survivorship and epidemiology (CASE): Interim results from a prospective study of the safety and effectiveness of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC) in a real-world setting.

Soo J. Park, Guilherme Rabinowits, Timothy J. Panella, Jade Homsi, Emily S. Ruiz, David M. Ellison, Michael J. Kelley, Yvonne M. Saenger, Richard Zuniga, Cong Zhu, Debra AG McIntyre, Ruben GW Quek, Joy Wang, Kathryn Gillis, Jean-Francois Pouliot, Nikhil I. Khushalani; Department of Medicine, Division of Hematology and Oncology, University of California San Diego, San Diego, CA; Department of Hematology and Oncology, Miami Cancer Institute/Baptist Health South Florida, Miami, FL; University of Tennessee Medical Center, Knoxville, TN; Division of Hematology and Oncology, UT Southwestern Medical Center, Dallas, TX; Department of Dermatology, Brigham and Women's Hospital, Boston, MA; Charleston Oncology, Charleston, SC; Durham VA Medical Center and Duke University School of Medicine, Durham, NC; Albert Einstein College of Medicine/Montefiore Medical Center, New York, NY; New York Cancer and Blood Specialists, New York, NY; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; Moffitt Cancer Center, Tampa, FL

Background: Cemiplimab is the first PD-L1 inhibitor approved for the treatment of patients with locally advanced (la) or metastatic (m) cutaneous squamous cell carcinoma (CSCC) not amenable to curative therapy. Here, we present an analysis of cemiplimab-treated patients with advanced CSCC enrolled in the CASE study (NCT03836105). **Methods:** CASE is a phase IV, multicenter, prospective, noninterventional study evaluating the effectiveness and safety of cemiplimab in patients with laCSCC/mCSCC and basal cell carcinoma. Data were collected from participating US academic and community oncology centers treating patients ≥18 years of age with intravenous cemiplimab per standard of care. The protocol was reviewed and approved by an institutional review board/ethics committee at each site and patients provided informed consent for study participation. Effectiveness outcomes included investigator-assessed (both physical and radiological) ORR (CR plus partial response) and progression-free survival (PFS). Safety outcomes included treatment-related immune-related adverse events (irAEs), infusion-related reactions (IRRs), and serious adverse events (SAEs). **Results:** As of December 4, 2024, 254 patients (including 44 [17%] immunocompromised/immunosuppressed) across 65 centers with advanced CSCC received ≥1 dose of cemiplimab. Median duration of exposure was 35 weeks (interquartile range: 15.0, 65.9). Most patients were aged ≥65 years (82.7%), male (78.3%), and white (89.0%). Demographics and disease characteristics were similar to those from the EMPOWER-CSCC-1 trial, with the exception of patients with Eastern Cooperative Oncology Group Performance Status of 2-3, which were excluded from the trial but represented 10.7% (27/254) of our real-world study analysis set. 64.2% of patients had laCSCC and 35.8% had mCSCC. ORR, including all patients regardless of missing response data, was 111/254 (43.7%; 95% CI: 37.5, 50.0) patients. CR was reached by 40/254 (15.7%) patients. ORR in patients with at least 1 response assessment reported was 111/201 (55.2%; 95% CI: 48.1,62.2) patients, and CR was reached by 40/201 (19.9%) patients. The overall response rate of the clinical trial (52.7%) fell within the range of our response data (43.7-55.2%). Median PFS was 14.7 (95% CI: 12.5, 21.1) months, with survival at 12 months estimated at 59.5% (95% CI: 51.4, 66.7). Treatment-related irAEs occurred in 76/254 (29.9%) patients and treatment-related SAEs occurred in 19/254 (7.5%) patients; one patient reported an IRR. **Conclusions:** The interim results of this Phase IV study demonstrate robust effectiveness and a generally manageable safety profile of cemiplimab in patients with laCSCC/mCSCC in real-world practice that are comparable to the results of the EMPOWER-CSCC-1 trial. Clinical trial information: NCT03836105. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Biosafety analysis from the skin cancer cohorts in the IGNYTE clinical trial of RP1.

Trisha Michel Wise-Draper, Caroline Robert, Michael K.K. Wong, Joseph J. Sacco, Gino Kim In, Eva Muñoz Couselo, Dirk Schadendorf, Georgia Beasley, Jiaxin Niu, Bartosz Chmielowski, Mohammed M. Milhem, Tawnya Lynn Bowles, Katy K. Tsai, Celeste Lebbe, Caroline Gaudy-Marqueste, Junhong Zhu, Jeannie Whit-Shan Hou, Robert S. Coffin, Aaron Clack, Praveen Bommareddy; University of Cincinnati Cancer Center, University of Cincinnati, Cincinnati, OH; Gustave Roussy and Paris-Saclay University, Villejuif, France; Roswell Park Comprehensive Cancer Center, Buffalo, NY; The Clatterbridge Cancer Centre and University of Liverpool, Wirral and Liverpool, United Kingdom; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron Hospital Medical Oncology Department, Barcelona, Spain; West German Cancer Center, University Hospital Essen, Essen, Germany; Duke Cancer Institute, Duke University, Durham, NC; Banner MD Anderson Cancer Center, Gilbert, AZ; Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA; Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; Intermountain Medical Center, Murray, UT; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; Université Paris Cité, AP-HP Dermato-Oncology and CIC, Cancer Institute APHP. Nord–Université Paris Cité, INSERM U976, Saint Louis Hospital, Paris, France; Aix-Marseille Université, APHM, Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM, U1068, CNRS, UMR7258, UM105, Hôpital Timone, CEPCM, Dermatology and Skin Cancer Department, Marseille, France; Replimune, Inc., Woburn, MA

Background: RP1 (vusolimogene oderparepvec) is an HSV–based oncolytic immunotherapy administered intratumorally. RP1 + nivolumab (nivo) has demonstrated deep, durable responses with favorable safety in advanced melanoma. We report biodistribution and shedding data from the skin cancer cohorts of the IGNYTE trial (NCT03767348). **Methods:** Following RP1 injection into superficial and/or deep lesions, injection sites were covered with occlusive dressings. Injection sites, dressings and mucosa were swabbed, and blood and urine were collected pre-dose, during treatment, and at follow-up visits. Samples were assessed for RP1 DNA by qPCR. Swab samples positive for RP1 DNA were further assessed by TCID50 assay for live RP1. **Results:** The highest incidence of RP1 DNA was from injection-sites where RP1 was detected in ~35% of samples for up to 15 days post-injection. Blood samples showed the presence of low copy numbers of RP1 DNA (122/1573 [7.8%]) in ~20% (53/274) of pts during or after RP1 treatment. The highest levels were detected in blood within 6 hours of injection and decreased thereafter. RP1 was only very rarely detected and at low copy number in urine samples (3/1976 [0.2%]) from 0.7% (2/273) pts at 15 days post-injection, with all subsequent samples testing negative. RP1 DNA was detected on injection-site dressing exteriors less often (9.5% of 1114 samples) than from injection sites (18.4% of 1947 samples), demonstrating that the dressings act as a barrier to RP1. RP1 DNA was rarely present on oral mucosa (0.9% of 2052 samples). At follow-up (30-100 days post last dose), RP1 DNA was detected only at injection-sites. All available samples were negative for live RP1 by TCID50. Eight swab samples from 7 pts were collected from suspected herpetic infections but all tested negative for live RP1. There were no reports of systemic herpetic infections in pts, nor of transmission to contacts. **Conclusions:** RP1 DNA was primarily detected on the surface of injected lesions for up to 15 days, with no live RP1 being detected at 30, 60 and 100 days post the last RP1 dose. Collectively, these data demonstrate that RP1 is rapidly cleared from blood and urine, with negligible likelihood of environmental dissemination or transfer to contacts, and that the use of occlusive dressings contains RP1.Defining the biodistribution and shedding of RP1 is relevant to the education of healthcare providers and to the development of best practices for the proper administration, handling and clean down. Clinical trial information: NCT03767348. Research Sponsor: Replimune, Inc.

9535 Poster Session

Clinical and biomarker analyses of first-line nivolumab and relatlimab (nivo-rela) in advanced or resectable melanoma (mel).

Lilit Karapetyan, Kimberly Ward, Shaliz Aflatooni, Denise Kalos, Carlos Moran-Segura, Bethany Withycombe, Pei-Ling Chen, Kenneth Yee Tsai, Jane Messina, Matthew Perez, Amod Sarnaik, Jonathan S. Zager, Rogerio Izar Neves, Vernon K. Sondak, Keiran Smalley, Joseph Markowitz, Andrew Scott Brohl, Zeynep Eroglu, Ahmad A. Tarhini, Nikhil I. Khushalani; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Moffitt Cancer Center - McKinley Campus, Tampa, FL; University of South Florida, Tampa, FL; Moffitt Cancer Center, Tampa, FL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Simultaneous blockade of lymphocyte activation gene-3 (LAG-3) and programmed death-1 (PD-1) pathways enhances antitumor activity in patients (pts) with mel. While efficacy of nivo-rela has been demonstrated in a large cohort of therapy-naïve advanced mel, it remains important to assess clinical activity of this combination in real-world settings focusing on resectable mel and on tumor microenvironment (TME) factors impacting response to nivo-rela. In this study we report the clinical activity of nivo-rela and the relation of TME characteristics to response to therapy. **Methods:** This study included pts with mel treated with first-line nivo-rela in the neoadjuvant or advanced settings between 2022-2024 at Moffitt. Safety, progression-free (PFS), overall survival (OS) and pathologic response rates were evaluated in relation to mel characteristics. To assess the impact of TME on response to nivo-rela in advanced mel, we performed NanoString GeoMx proteomic analysis using immune cell profiling, immune cell typing, and IO drug target panels. Differential proteomic analysis (fold change $\geq$0.05, FDR $<$0.05) was performed using selected baseline samples (n=16) from responders (R) and non-responders (NR). **Results:** The study included 128 mel pts treated with nivo-rela in the advanced (n=101, [C1]) and neoadjuvant (n=27, [C2]) settings, 48 female (38%) and 80 male (62%), median age 71 [IQR 62–78]. In C1, with a median follow up of 13 months, mPFS and mOS with 95% CI were 19m (10-NR), and NR (25-NR), respectively. In C2, 6 (22%) of pts did not undergo definitive surgery due to disease progression (n=4) and clinical response to therapy (n=2). Among path-evaluable pts (n=21), major pathologic response rate was 10 (48%) including 6 complete (29%) and 4 near-complete responses 19%), with partial response in 3 (14%) and non-response in 8 patients (38%). Adverse events included adrenal insufficiency and myocarditis in 12 (9%) and 4 (3%) of all pts. TME assessment revealed no significant differences in expression of LAG3, PD-1, PDL-1, $CD8^+$ among R vs NR. Baseline tumors from NR were characterized by high expression of B7-H3 in both tumor and immune compartments. No significant correlations were found between B7-H3 and PDL-1, LAG-3, and CTLA-4. High B7-H3 ROIs were enriched by $CD163^+$, $CD68^+$, $CD14^+$, and fibroblast activation protein alpha. **Conclusions:** In a real-world setting, first-line nivo-rela in advanced mel resulted in potentially better PFS while in resectable pts the major pathologic response rate was lower than previously reported in clinical trials. Mel TME with high B7-H3 protein expression was enriched with M2-skewed macrophages and fibroblasts in association with non-response to nivo-rela. This finding warrants further investigation of B7-H3 targeting agents in mel pts. Research Sponsor: None.

Final results of POD1UM-201, a phase 2 study of retifanlimab, a humanized anti–PD-1 antibody, in patients with advanced or metastatic Merkel cell carcinoma (MCC).

Giovanni Grignani, Piotr Rutkowski, Celeste Lebbe, Michele Guida, Caroline Gaudy-Marqueste, Filippo Guglielmo Maria De Braud, Francesco Spagnolo, Melissa Amber Burgess, Henri Montaudie, Roberta Depenni, Francesca Spada, Jennifer Pulini, Mark J. Cornfeld, Chuan Tian, Shailender Bhatia; Candiolo Cancer Institute, FPO – IRCCS, Candiolo, Torino, Italy; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Université de Paris, Department of Dermatology and CIC, AP-HP Hôpital Saint-Louis, Paris, France; Melanoma and Rare Tumors Unit, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy; Aix-Marseille University, AP-HM, Hopital Timone, Dermatology and Skin Cancer Department, Marseille, France; Fondazione IRCCS Istituto Nazionale dei Tumori, Università di Milano, Milan, Italy; Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy; UPMC Hillman Cancer Center, Pittsburgh, PA; Department of Dermatology, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France; Department of Oncology and Haematology, Division of Oncology, University Hospital of Modena, Modena, Italy; Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology (IEO), IRCCS, Milan, Italy; Incyte Corporation, Wilmington, DE; Division of Medical Oncology, Department of Medicine, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA

Background: Retifanlimab is approved in the United States and Europe for treatment of adults with metastatic or recurrent locally advanced MCC, based on previously reported results from the open-label single-arm POD1UM-201 study (NCT03599713). As previously reported, objective response rate (ORR) was 54% (95% confidence interval [CI], 43, 64) and probability of remaining progression free at 12 months was 71% (Grignani G, et al. *Ann Oncol.* 2023;34(suppl 2):S686). Safety profile was as expected for the PD-(L)1 inhibitor class. Here, we present the final results from POD1UM-201 based on extended follow-up. **Methods:** Eligible patients were aged ≥18 years with metastatic or recurrent unresectable locoregional MCC, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Prior systemic treatment for MCC was not allowed. Retifanlimab 500 mg was administered intravenously once every 4 weeks for up to 2 years. Premedication prophylaxis was not routinely administered. The primary endpoint was ORR assessed by independent central review per RECIST v1.1. Key secondary endpoints were duration of response (DOR), disease control rate, progression-free survival, overall survival, and safety. **Results:** The study enrolled 101 patients in North America and Europe between February 12, 2019, and June 16, 2021. Patients had a median age of 71 (range: 38, 90) years, 68 (67%) were male, 77% were White, 74 (73%) had an ECOG PS of 0, and 1 (1%) patient was HIV positive. 91 patients (90%) had stage IV disease, 69 (68%) had prior surgery, and 37 (37%) had prior radiotherapy. Merkel cell polyomavirus and PD-L1 expression were detectable in 73 (72%) and 83 (82%) patient tumor samples, respectively. Median follow-up duration was 36 (range: 1, 60) months. Summary efficacy results are shown in the Table. ORR was 55% (95% CI, 44, 64), with complete response observed in 18 patients (18%). Median DOR was not reached and probability of remaining progression free at 36 months was 57%. Most common immune-related adverse events (irAEs) were skin reactions (10%), including pruritus (4%) and rash (3%), and hypothyroidism (8%); 11% of patients had grade ≥3 irAEs and 9% discontinued treatment due to irAEs. **Conclusions:** Retifanlimab is a highly active treatment for advanced MCC with a safety profile that is representative of the PD-(L)1 inhibitor class. Clinical trial information: NCT03599713. Research Sponsor: Incyte Corporation.

Summary of efficacy.

Study Endpoint	N=101
Overall response rate (95% CI), %	55 (44, 64)
Complete response, n (%)	18 (18)
Partial response, n (%)	37 (37)
Disease control rate (95% CI), %	60 (50, 70)
Duration of response, median (range), months	NR (23, NE)
Progression-free survival, median (range), months	16 (9, 32)
Overall survival, median (range), months	NR (45, NE)

CI, confidence interval; NE, not estimable; NR, not reached.

9537 Poster Session

Response analysis for injected and non-injected lesions and of the safety and efficacy of superficial and deep/visceral RP1 injection in the registrational cohort of anti–PD-1–failed melanoma patients of the IGNYTE trial.

Gino Kim In, Michael K.K. Wong, Joseph J. Sacco, Eva Muñoz Couselo, Dirk Schadendorf, Georgia Beasley, Jiaxin Niu, Bartosz Chmielowski, Trisha Michel Wise-Draper, Mohammed M. Milhem, Tawnya Lynn Bowles, Katy K. Tsai, Celeste Lebbe, Caroline Gaudy-Marqueste, Adel Samson, Junhong Zhu, Marcus Viana, Jeannie Whit-Shan Hou, Caroline Robert; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Roswell Park Comprehensive Cancer Center, Buffalo, NY; The Clatterbridge Cancer Centre and University of Liverpool, Wirral and Liverpool, United Kingdom; Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron Hospital Medical Oncology Department, Barcelona, Spain; West German Cancer Center, University Hospital Essen, Essen, Germany; Duke Cancer Institute, Duke University, Durham, NC; Banner MD Anderson Cancer Center, Gilbert, AZ; Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA; University of Cincinnati Cancer Center, University of Cincinnati, Cincinnati, OH; Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; Intermountain Medical Center, Murray, UT; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; Université Paris Cité, AP-HP Dermato-Oncology and CIC, Cancer Institute APHP. Nord–Université Paris Cité, INSERM U976, Saint Louis Hospital, Paris, France; Aix-Marseille Université, APHM, Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM, U1068, CNRS, UMR7258, UM105, Hôpital Timone, CEPCM, Dermatology and Skin Cancer Department, Marseille, France; Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, United Kingdom; Replimune, Inc., Woburn, MA; Gustave Roussy and Paris-Saclay University, Villejuif, France

Background: The IGNYTE trial (NCT03767348) primary analysis of RP1 (vusolimogene oderparepvec) plusnivolumab (nivo) showed clinically meaningful durable efficacy (ORR, 32.9%; median DOR, 33.7 mos, by RECIST 1.1 and independent central review) in patients (pts) with advanced melanoma, including deep responses in non-injected visceral lesions, demonstrating systemic efficacy. Here we present an analysis of efficacy in injected and non-injected lesions and safety and efficacy in pts receiving superficial and/or deep/visceral RP1 injections. **Methods:** Pts with confirmed progression during anti–PD-1 ± anti–CTLA-4 for ≥8 weeks were enrolled. RP1 (1×10^6 PFU/mL x1, then Q2W 1×10^7 PFU/mL x7, up to 10 mL) was injected into superficial and/or deep/visceral tumors using imaging guidance. Nivo was given (240 mg Q2W) from the 2nd dose of RP1 through dose 8, then alone (240 mg Q2W or 480 mg Q4W) for 2 yrs, with additional RP1 injections allowed if indicated. **Results:** For the 46 responding patients by RECIST 1.1 (of the 140 enrolled) 197 lesions were measured, 78 injected, 119 non-injected of which 98.7% and 96.6% had any reduction and 93.5% and 79.0% >30% reduction, respectively. For visceral lesions, 85.7% of injected and 96.2% of non-injected lesions had any reduction and 85.7% and 65.4% had >30% reduction, respectively. 104 patients had superficial only injections, and 36 had deep/visceral +/- superficial injections. Treatment-related adverse event (TRAEs) rates were comparable in patients who were injected superficially compared to patients who received deep/visceral injections, except for chills, influenza-like illness, and injection-site pain, which were numerically higher in the deep/visceral +/- superficial group. Grade ≥3 TRAEs occurred in 14.4% of pts by superficial injection and 8.3% by deep/visceral +/- superficial injection. Grade 1/2 pneumothorax occurred in 3/52 (5.8%) lung injections. No liver function abnormalities or significant bleeds were reported after liver injections. The ORR for pts with superficial injection only was 29.8%, and 41.7% for deep/visceral +/- superficial. **Conclusions:** Meaningful systemic responses were observed independent of the injection status of individual lesions or their anatomical site. Overall response was therefore driven by the response of both injected and non-injected lesions. The safety profile of deep/visceral injection was comparable to that of superficial injections, with efficacy also being similar. Clinical trial information: NCT03767348. Research Sponsor: Replimune, Inc.

Long-term outcomes after discontinuation of retifanlimab in patients with advanced or metastatic Merkel cell carcinoma (MCC) in the POD1UM-201 trial.

Giovanni Grignani, Piotr Rutkowski, Celeste Lebbe, Michele Guida, Caroline Gaudy-Marqueste, Federica Morano, Francesco Spagnolo, Melissa Amber Burgess, Henri Montaudie, Roberta Depenni, Francesca Spada, Jennifer Pulini, Mark J. Cornfeld, Xiaohan Xu, Shailender Bhatia; Candiolo Cancer Institute, FPO – IRCCS, Candiolo, Torino, Italy; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Université de Paris, Department of Dermatology and CIC, AP-HP Hôpital Saint-Louis, Paris, France; Melanoma and Rare Tumors Unit, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy; Aix-Marseille University, AP-HM, Hopital Timone, Dermatology and Skin Cancer Department, Marseille, France; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; IRCCS Ospedale Policlinico San Martino, Genoa, Italy; UPMC Hillman Cancer Center, Pittsburgh, PA; Department of Dermatology, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France; Department of Oncology and Haematology, Division of Oncology, University Hospital of Modena, Modena, Italy; Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology (IEO), IRCCS, Milan, Italy; Incyte Corporation, Wilmington, DE; Division of Medical Oncology, Department of Medicine, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA

Background: Retifanlimab is a humanized programmed cell death protein-1 (PD-1)–blocking antibody that is approved for treatment of adults with metastatic or recurrent locally advanced MCC in the United States and Europe. Approval was based on primary results from the phase 2, open-label, single-arm POD1UM-201 study (NCT03599713). Here, we present long-term outcomes in patients with MCC who discontinued retifanlimab for reasons other than confirmed disease progression, as previous studies have suggested high rates of recurrence in patients discontinuing treatment after initial response. **Methods:** POD1UM-201 enrolled patients with metastatic or recurrent unresectable locoregional MCC who had not received prior systemic treatment. Retifanlimab was administered every 4 weeks (q4w) intravenously (IV) for a maximum of 2 years, or until progressive disease (PD) or unacceptable toxicity. Patients with complete response (CR) were permitted to discontinue treatment after a minimum of 6 months at investigator discretion. Patients who discontinued retifanlimab for reasons other than PD were closely followed for disease status by independent central review (ICR) until disease progression or death. **Results:** The study enrolled 101 patients with a median (range) follow-up duration of 36 (1, 60) months. Objective response rate was 55% and disease control rate was 60%, including 18 patients (18%) with CR, 37 (37%) with partial response (PR), and 6 (6%) with stable disease (SD) for ≥6 months. Sixty-four patients (63%) discontinued treatment prior to completion of therapy, most commonly due to tumor progression. Forty-one patients were continuing to demonstrate ICR confirmed benefit when treatment was discontinued (CR, n=15; PR, n=21; SD, n=5). Of these patients, 26 (63%) completed the protocol-defined maximum 2 years of therapy, 3 (7%) discontinued at the discretion of the investigator after CR was achieved, and 12 (29%) discontinued due to toxicity. Among the patients with CR or PR, 30 (83%) were alive without disease progression at time of last follow-up after a median (range) of 18 (2, 46) months. Patients who achieved a CR or PR had a lower rate of PD or death compared with those with SD; 7% of patients with a CR experienced PD during follow-up vs 24% of patients with a PR and 60% of patients with SD. **Conclusions:** Retifanlimab 500 mg administered q4w IV for up to 2 years led to durable clinical responses in the majority of patients with advanced MCC. Most patients with an ongoing objective response (CR or PR) remain progression free beyond discontinuation of therapy, suggesting sustained benefit is possible in patients with this highly aggressive disease. Clinical trial information: NCT03599713. Research Sponsor: Incyte Corporation.

9539 Poster Session

Updated analyses from a global meta-analysis in metastatic uveal melanoma (mUM) to determine progression free and overall survival benchmarks by line of therapy: An international rare cancers initiative (IRCI) ocular melanoma study.

Leila Khoja, Eshetu G. Atenafu, Anthony M. Joshua, International Rare Cancers Initiative (IRCI) Ocular Melanoma Group; University of Birmingham, Birmingham, United Kingdom; Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada; Kinghorn Cancer Centre, Sydney, Australia

Background: PUMMA is an individual trial patient level meta-analysis that established survival and prognostic benchmarks in metastatic uveal melanoma (Khoja et al, 2019) in 912 patients treated 2000-2016. **Methods:** Herein we describe the dataset further by line of treatment to assist in establishing benchmarks of activity needed to satisfy synthetic control arm surrogates for regulatory purposes for benchmarks of PFS (Progression Free Survival) and OS (Overall Survival) in months (m). **Results:** Within the PUMMA dataset, 567 (62.2%) received 1st line treatment, 161 (17.7%) received 2^{nd} /3^{rd} line treatment. OS was comparable by line of treatment (P=0.2513) with 12m OS rates being 41.3% and 40.5% respectively. Median OS by line of treatment was 9.95 m (95% CI 9.23-10.74) for 1^{st} line and 10.15 m (7.69-11.60) for 2^{nd}/3^{rd} line. PFS was also comparable by line of treatment (p=0.51) with 12m PFS rates being 11.7% and 7.2% respectively. Median PFS by line of treatment was 2.76 m (95% CI 2.66-3.38) for 1^{st} line and 2.86 m (95% CI 2.73-3.52) for 2^{nd}/3^{rd} line. Multivariable analysis of the 1^{st} and 2^{nd}/3^{rd} line treatments separately suggested statistically significant ($p<0.05$) variables associated with inferior PFS in the first line setting included male sex, LDH>2X ULN, ALP>2X ULN whilst inferior PFS in the 2^{nd}/3^{rd} line was predicted by LDH>2X ULN only. Inferior OS in the 1^{st} line setting was statistically significantly associated with ECOG>2, Age > 65, male sex, LDH>2X ULN, ALP>2X ULN whilst inferior OS in the 2^{nd}/3^{rd} line was associated with ECOG>2, LDH>2X ULN, and ALP>2XULN. **Conclusions:** PUMMA continues to show value in providing benchmarks of activity for future clinical trials or regulatory purposes in mUM. The prognostic ability of LDH>2XULN retains important value across multiple lines of treatment scenarios in the PUMMA dataset. Research Sponsor: None.

A phase II, open-label study to improve compliance and time of treatment after obtaining complete response (CR) through a tailored schedule of sonidegib in locally advanced basal cell carcinomas (laBCC): The SONIBEC trial.

Carlo Resteghini, Sara Farinatti, Andrea Alberti, Valeria Tovazzi, Paola Queirolo, Maristella Saponara, Giuseppe Argenziano, Riccardo Marconcini, Ketty Peris, Paola Savoia, Maria Chiara Tronconi, Iris Zalaudek, Paolo Antonio Ascierto, Francesco Spagnolo, Luigi Lorini, Cristina Gurizzan, Paolo Bossi; Department of Biomedical Sciences, Humanitas University; IRCCS Humanitas Research Hospital, Pieve Emanuele, Italy; Medical Oncology Unit, Department of Medical & Surgical Specialties, Radiological Sciences & Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy; IRCCS Istituto Europeo di Oncologia, Milan, Italy; Dermatology Unit, University of Campania L. Vanvitelli, Naples, Italy; Medical Oncology Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Institute of Dermatology, Catholic University Fondazione Policlinico Universitario, Roma, Italy; Department of Health Sciences, University of Eastern Piedmont, Novara, Italy; IRCCS Humanitas Research Hospital, Rozzano, Rozzano, Italy; Department of Dermatology and Venereology of the Medical University of Triest, Trieste, Italy; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Department of Medical Oncology, IRCCS Ospedale Policlinico San Martino, Genova, Italy; IRCCS Humanitas Research Hospital, Rozzano, Italy

Background: Sonidegib is an efficacious treatment of LA laBCC but is associated with a high risk of treatment-related adverse events (TRAEs) causing treatment discontinuation. Following a CR, treatment discontinuation rate reaches up to 60% after a year, leading to 3 years relapse free survival rate of 35%. We aimed at evaluating sonidegib tailored schedule (TS) after CR to increase treatment duration by reducing TRAEs, thus allowing CR maintenance. **Methods:** We conducted a multicenter, open-label, single-arm phase II study enrolling adult patients (pts) with laBCC who obtained a CR to sonidegib regardless of the tumor's subtype and burden. Eligible pts received TS1 with sonidegib 14 days on and 14 days off. Pts on TS1 who experienced grade 2-3 toxicity (except alopecia) lasting >28 days moved to TS2 (7 days on and 21 days off). Treatment continued until progression or unacceptable toxicity. Primary endpoint was the rate of pts maintaining sonidegib 12 months after study enrolment (H0 31%, H1 60%). Evaluable pts were defined as all pts who were either on treatment or suspended treatment for reasons other than treatment-unrelated adverse events or death. Secondary endpoints were safety, treatment compliance, rate of disease relapse at 1 and 2 years, overall survival, quality of life, use of concomitant medications and of medical resources, and translational analysis. **Results:** Between Jan 2021 and Dec 2023, 22 pts from 10 Italian centers were enrolled; the data cut-off was Jan 2025. Pts characteristics are reported in table 1. The median follow-up was 22 months (range 2-33). Three disease and treatment-unrelated deaths occurred before completing 1 year of TS and therefore 19 pts were evaluable. At data cut-off, 12 pts had discontinued treatment: 26% (5) due to disease progression, 11% (2) to sonidegib's unacceptable toxicity, the remaining either to personal or physician's choice. Twelve out of 19 evaluable pts (63%) were still on treatment after 1 year from TS start (median duration 20 months, range 2-29), meeting the primary endpoint. The most common TRAEs episodes were muscle cramps (13), alopecia (6), dysgeusia (5) with overall TRAEs grade G1 (29), G2 (11), G3 (3). Twelve pts had dose reduction to TS2. **Conclusions:** Tailored maintenance schedule with pulsed sonidegib allows for longer treatment duration and fewer relapses in CR laBCC pts. Study follow up to evaluate secondary endpoints outcome and translational analysis are ongoing. Clinical trial information: 2020-002613-17. Research Sponsor: This is an investigator initiated trial partially supported by an unconditional grant by SunPharma.

Patient characteristics.

Characteristic	N (%)
Male : Female	14 (64) : 8 (36)
Median age	76y (range 56-93y)
ECOG PS 0-1	15 (68): 7 (32)
Histology sub-type	
Nodular	8 (36)
Superficial	2 (9)
Infiltrative	7 (32)
Mixed	1 (5)
Other	4 (18)

9541 Poster Session

AI-detected tumor-infiltrating lymphocytes and response to PD-1 based treatment in advanced melanoma.

Mark Schuiveling, Isabella A.J. van Duin, Laurens ter Maat, Janneke C. van der Weerd, Franchette van den Berkmortel, Femke Burgers, Marye J. Boers-Sonderen, Alfonsus Johannes Maria van den Eertwegh, Jan Willem de Groot, John Haanen, Geke Hospers, Ellen Kapiteijn, Djura Piersma, Gerard Vreugdenhil, Hans M. Westgeest, Anne M.R. Schrader, Mitko Veta, Willeke Blokx, Paul J. van Diest, Karijn Suijkerbuijk; University Medical Center Utrecht, Utrecht, Netherlands; University Medical Center Groningen, Groningen, Netherlands; Zuyderland Medical Center, Heerlen, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands; Amsterdam UMC, location VUMC, Cancer Center Amsterdam, Amsterdam, Netherlands; Isala Oncology Center, Zwolle, Netherlands; Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands; Medisch Spectrum Twente, Enschede, Netherlands; Maxima Medical Center, Eindhoven, Netherlands; Amphia Hospital, Breda, Netherlands; Leiden University Medical Center, Leiden, Netherlands; Eindhoven University of Technology, Eindhoven, Netherlands

Background: Biomarkers to predict response to immune checkpoint inhibition (ICI)-treated melanoma are limited. This study evaluates AI-detected tumor-infiltrating lymphocytes (TILs) on pretreatment metastatic pathology specimens as a biomarker for response and survival in ICI-treated patients. **Methods:** Patients treated with first-line anti-PD1 ± anti-CTLA4 for advanced melanoma were retrospectively identified from 11 Dutch melanoma centers. Pre-treatment TILs were quantified on H&E stained slides using the Hover-NeXt algorithm trained on an independent melanoma dataset with 166.718 pathologist checked manually annotated cells. The average percentage of TILs per 200 μm^2 tumor area was calculated. The primary outcome was response to ICI per RECIST 1.1 with overall survival (OS) and progression free survival (PFS) as secondary outcomes. Univariable and multivariable logistic and Cox regression analyses assessed associations between a 10% increase in TILs present in pre-treatment metastatic slides and clinical outcomes. Multivariable analyses were adjusted for age, sex, disease stage, BRAF mutation, LDH and performance score. Objective response rate and Kaplan Meier survival analysis were stratified by TIL tertiles. **Results:** Metastatic melanoma specimens were available for 1246 patients, 441 received anti-PD1 + anti-CTLA4. Median TIL percentage was 10.2% (interquartile range 5.5% – 17.2%). A 10% higher baseline TIL percentage was associated with response (adjusted OR 1.39 [95% 1.21-1.58]), PFS (adjusted HR 0.87 [95% CI 0.81 – 0.94]) and OS (adjusted HR 0.84 [95% CI 0.77 – 0.93] in univariable and multivariable analysis (Table 1). Stratified analysis showed significant associations between TILs, response, and survival in both anti-PD1 monotherapy and combination therapy. **Conclusions:** AI-quantified TILs in pre-treatment melanoma metastases are correlated with improved response rates and survival in ICI treated patients. This correlation is independent of known clinical predictors. Research Sponsor: The Netherlands Organization for Health Research and Development (ZonMW); 848101007; Stichting Hanarth Fonds.

Outcome	ICI	Lowest Tertile	Middle Tertile	Highest Tertile	Univariable OR / HR [95% CI]	Multivariable OR / HR [95% CI]
Response (%)	All	47.9%	57.8%	64.5%	1.35 [1.21 – 1.52]	1.39 [1.21 – 1.58]
	Anti-PD1	45.2%	57.1%	66.7%	1.42 [1.24 – 1.64]	1.37 [1.17 – 1.60]
	Anti-PD1 + Anti-CTLA4	51.4%	62.2%	58.7%	1.23 [1.00 – 1.53]	1.48 [1.13 – 1.94]
PFS (months)	All	5.4	9.7	15.3	0.87 [0.81 – 0.93]	0.87 [0.81 – 0.94]
	Anti-PD1	5.4	11.8	16.5	0.85 [0.79 – 0.92]	0.89 [0.81 – 0.97]
	Anti-PD1 + Anti-CTLA4	5.3	11.0	10.2	0.89 [0.78 – 1.02]	0.80 [0.69 – 0.94]
OS (months)	All	21.4	38.4	49.2	0.81 [0.75 – 0.88]	0.84 [0.77 – 0.93]
	Anti-PD1	21.1	36.5	51.4	0.79 [0.71 – 0.87]	0.86 [0.77 – 0.96]
	Anti-PD1 + Anti-CTLA4	21.4	77.8	46.4	0.88 [0.75 – 1.03]	0.82 [0.69 – 0.97]

9542 Poster Session

Real-world clinical outcomes of patients with BRAF-mutated melanoma with or without brain metastases receiving frontline immune-checkpoint inhibitors in the US community oncology setting.

Wolfram Samlowski, Andrew J. Osterland, Lisa Herms, Malcolm Charles, Matthew Whitesell, Janet L. Espirito; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Ontada, Boston, MA

Background: Patients with BRAF-mutated melanoma are at increased risk of melanoma brain metastasis (MBM) which has historically led to worse outcomes. The prognosis of patients with MBM has improved with approval of immune checkpoint inhibitors (ICI) and targeted therapy. However, there is limited information on the impact of the MBM on outcomes in patients with BRAF mutations treated with frontline (1L) ICI. This study aims to describe clinical outcomes of patients with BRAF-mutated metastatic melanoma treated with 1L ICI in the community oncology setting, with a focus on patients with MBM. **Methods:** This was a retrospective observational cohort study of patients with BRAF-mutated metastatic melanoma who initiated 1L ICI (index) between 1/1/16-6/30/22 in The US Oncology Network and non-Network practices and were followed through 6/30/24. Patient characteristics and genomic alterations were sourced from structured electronic health records data and genomic testing results. Patients with mucosal or uveal melanoma, clinical trial participation, treatment for other primary cancers or evidence of co-mutations were excluded. Kaplan-Meier analyses of overall survival (OS), real-world time to treatment discontinuation (rwTTD) and time to next treatment (rwTTNT) were assessed from index, overall and in patients with MBM. **Results:** Of 798 metastatic melanoma patients with a BRAF mutation, 41 (5%) had documentation of a co-mutation and were excluded, resulting in 757 patients in the final analysis set. Median follow-up was 14.6 months, and median age at index was 64 years. Among patients with available data, most were male (63%), White (97%) and had an ECOG of 0-1 (87% among reported) within 60 days prior to index. Among patients with mutation-specific data (n=704), the most common mutation types were V600E (83%) and other V600 (13%) point mutations. The most common 1L ICI regimens were nivolumab+ipilimumab (45%), pembrolizumab (30%), and nivolumab (22%). MBM was documented in 46 (6%) patients at 1L ICI treatment initiation, and an additional 28 (4%) patients developed MBM during the follow-up period, resulting in a total of 74 (10%) patients with MBM. **Conclusions:** Although lower-than-expected rates of MBM were observed, in this large real-world dataset from the community setting, patients with a BRAF mutation had similar rwTTD, rwTTNT, and OS following ICI therapy, irrespective of the presence of MBM. It is reasonable to consider combination ICI therapy in BRAF mutant melanoma patients diagnosed with MBM who lack known contraindications. Further research on the impact of the somatic mutational background on MBM outcomes is ongoing. Research Sponsor: None.

Outcome, median (95% CI)	Overall (N=757)	MBM, any time (N=74)
OS, months	20.3 (16.6, 25.8)	20.3 (10.4, 33.8)
rwTTD, months	3.5 (2.9, 3.9)	3.7 (2.4, 5.6)
rwTTNT, months	5.7 (4.9, 6.5)	5.6 (3.7, 7.5)

9543 Poster Session

Real-world safety and effectiveness of avelumab in immune-compromised (IC) and non-IC patients with Merkel cell carcinoma (MCC): Results from a prospective German registry (MCC-TRIM).

Jurgen Becker, Seyed Hamidreza Mahmoudpour, Dirk Schadendorf, Ulrike M. Leiter, Friedegund Elke Meier, Rudolf Alexander Herbst, Stephan Grabbe, Christoffer Gebhardt, Fabian Ziller, Claudia Pföhler, Peter Mohr, Lisa Zimmer, Emmanuelle Boutmy, Dina Oksen, Mairead Kearney, Katia Ruth, Sebastian Hoff, Margarita Shlaen, Selma Ugurel; University Hospital Essen, German Cancer Consortium (DKTK), Partner Site Essen/Düsseldorf, German Cancer Research Center (DKFZ), Heidelberg, Germany; The Healthcare Business of Merck KGaA, Darmstadt, Germany; University of Essen and the German Cancer Consortium, Essen, Germany; Department of Dermatology, Center for Dermatooncology, Eberhard Karls University of Tübingen, Tübingen, Germany; Department of Dermatology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Skin Cancer Center at the University Cancer Centre Dresden and National Center for Tumor Diseases, Dresden, Germany; Department of Dermatology, Helios Klinikum Erfurt, Erfurt, Germany; Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; Department of Dermatology/Skin Cancer Center, University Medical Center Hospital Hamburg-Eppendorf, Hamburg, Germany; Department of Dermatology, DRK Krankenhaus Rabenstein, Chemnitz, Germany; Department of Dermatology, Saarland University Medical School, Homburg/Saar, Germany; Department of Dermatology, Elbe-Kliniken, Buxtehude, Germany; Department of Dermatology, University Hospital Essen; German Cancer Consortium, Partner Site Essen; National Center for Tumor Diseases (NCT), NCT-West, Campus, Essen, Germany; IQVIA Commercial GmbH & Co. OHG, München, Germany; Department of Dermatology, University Hospital Essen, University of Duisburg-Essen & German Cancer Consortium, Heidelberg, Germany

Background: MCC is a rare and aggressive form of skin cancer. Avelumab was the first immunotherapy approved for patients with metastatic MCC in Europe. Immunosuppression is an established risk factor for developing MCC, but IC patients have typically been excluded from clinical trials of immunotherapies. We report an analysis of clinical characteristics, survival outcomes, and safety in IC and non-IC patients with MCC treated with avelumab in routine clinical practice in Germany. **Methods:** This prospective, noninterventional, multicenter, dynamic cohort study (MCC-TRIM; EUPAS25338) enrolled patients with MCC in Germany between April 2019 and September 2023. Primary data from a study-specific electronic case report form and secondary data from the German national skin cancer registry were combined. For this analysis, avelumab-treated patients were grouped as IC or non-IC based on prespecified comorbid conditions and concomitant medications. Survival outcomes with first-line avelumab treatment were assessed using the Kaplan-Meier method. **Results:** Among 875 patients with MCC (various disease stages) enrolled in the study, 243 were treated with avelumab, of whom 189 (77.8%) were considered non-IC and 54 (22.2%) were considered IC. Patient characteristics are summarized in the Table. At data cutoff (March 2024), median follow-up (IQR) was 14.3 months (6.4-29.4) in the non-IC subgroup and 8.9 (4.2-22.8) in the IC subgroup. In non-IC and IC subgroups, median (95% CI) overall survival from start of first-line avelumab was 38.2 (15.7-not estimable) and 9.9 (4.8-29.8) months, and median progression-free survival was 7.9 (4.0-11.6) and 4.3 (1.0-7.8) months, respectively. The incidence rate of ADRs related to avelumab was 1.01 (95% CI, 0.75-1.34) events per person-year in the non-IC subgroup and 0.71 (95% CI, 0.32-1.45) events per person-year in the IC subgroup. **Conclusions:** Results from this German nationwide registry showed the safe and effective use of avelumab in routine clinical practice for IC and non-IC patients with MCC. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	Non-IC (n=189)	IC (n=54)
Mean age at diagnosis (SD), years	74.8 (10.2)	76.4 (8.1)
Male, n (%)	122 (64.6)	35 (64.8)
Stage at diagnosis, n (%)		
Early stage (I, II, or unknown)	38 (20.1)	13 (24.1)
III	80 (42.3)	19 (35.2)
IV	71 (37.6)	22 (40.7)
ECOG performance status ≤1, n (%)	153 (81.0)	40 (74.0)
Comorbidities, n (%)		
Diabetes	36 (19.0)	14 (25.9)
Chronic obstructive pulmonary disease	5 (2.6)	4 (7.4)
Cerebrovascular disease/stroke	2 (1.1)	3 (5.6)
Moderate or severe renal disease	11 (5.8)	5 (9.3)
Ischemic heart disease/myocardial infarction	21 (11.1)	8 (14.8)
Moderate or severe liver disease	3 (1.6)	0
Thyroid disorder	17 (9.0)	4 (7.4)
Inflammatory bowel disease	4 (2.1)	2 (3.7)
Rheumatoid arthritis	5 (2.6)	5 (9.3)

9545 Poster Session

Progression-free survival (PFS) assessment by blinded independent central review (BICR) versus local investigator (LI) in metastatic melanoma (MM) randomized controlled trials (RCT): A systematic review and meta-analysis.

Islam Eljilany, Eissa Jafari, Abdullah Alhumaid, Zeynep Eroglu, Joseph Markowitz, Lilit Karapetyan, Andrew Scott Brohl, Nikhil I. Khushalani, Patrick Hwu, Ahmad A. Tarhini; Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Department of Pharmacy Practice, College of Pharmacy, Jazan University, Jazan, Saudi Arabia; Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics and Precision Medicine, College of Pharmacy, University of Florida, Gainesville, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Although BICR may reduce assessment variability, it introduces additional financial and logistical burdens to trial operations. This study analyzed the discrepancy indexes (DIs) to evaluate differences between PFS assessments evaluated by LIs and BICR in RCTs of patients (pts) with MM. **Methods:** A comprehensive literature search was conducted on PubMed, Embase, and Cochrane databases until June 30, 2023. Studies were eligible for inclusion in the meta-analysis if they were 1) Phase II or III RCTs with accessible, published data; 2) inclusion of pts diagnosed with MM; 3) availability of PFS data assessed through both LI and BICR; and 4) publication in English. The study complied with the PRISMA guidelines to ensure methodological rigor. Two independent researchers performed data extraction to minimize bias and ensure accuracy. A fixed-effects meta-analysis approach was applied to summarize treatment outcomes, producing pooled estimates and corresponding 95% confidence intervals (CIs). The primary outcome was DI, which was calculated for each trial as a ratio of the hazard ratios $(HR)_{BICR}$ by HR_{LI}. The agreement between PFS HRs was also evaluated using the intraclass correlation coefficient (ICC) and Pearson's correlation coefficient (r). The risk of bias was evaluated using the Cochrane Risk of Bias tool v.2 (RoB 2). **Results:** A total of 12 studies comprising 4,915 pts were included in the meta-analysis that spanned from 2012 to 2023. Of these, 10 studies (83%) were Phase III , 11 (92%) were cutaneous melanoma and all identified PFS as the primary endpoint. Most studies (n = 8, 75%) had a DI $>$ 1 and the overall combined DI was 1.08 (95% CI: 1.01–1.15), indicating a statistically significant numerically small difference (8%) in PFS evaluations conducted by the two assessments, suggesting that BICR tended to be more conservative in PFS assessments. These results were primarily driven by the Phase II or double-blinded studies, which showed a higher median (inter-quartile range) (IQR) DI [1.14 (0.08) and 1.16 (0.13), respectively] than phase III or open-label trials [DI 1.04 (0.12) or 1.0 (0), respectively] . However, there was an overall significant strong correlation [ICC: 0.87, $p <$ 0.001); r= 0.89, 95% CI 0.67-0.96, $p <$0.0001)] between BICR and LI assessments and most (86%) of the PFS comparisons led to the same statistical inference. Finally, 10 studies had a low risk of systematic bias, and none had publication bias. **Conclusions:** This study demonstrated a slim statistically significant difference in PFS assessments between LI and BICR, but with strong agreements overall. These findings challenge the necessity of universally implementing BICR in all RCTs, supporting appropriate use in selected scenarios, primarily Phase II RCT. Also, supports the value of double-blinded studies. Research Sponsor: None.

9546 Poster Session

Efficacy and safety of transcatheter arterial infusion of immune checkpoint inhibitors in locoregional unresectable or in-transit acral melanoma: A multi-center real-world study.

Ziluan Chen, Lujun Shen, Weijun Fan, Xiaoshi Zhang, Dandan Li; Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Minimally Invasive Interventional Therapy, Liver Cancer Study and Service Group, Sun Yat-Sen University Cancer Center, Guangzhou, China; Sun Yat-Sen University Cancer Center, Guangzhou, China; Biotherapy Center, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Acral melanoma (AM) is highly invasive. Standard treatment options, including surgical resection and systemic immunotherapy, frequently yield insufficient control over local lesions. Although various local treatment strategies are currently available, such as isolated limb perfusion (ILP), isolated limb infusion (ILI), intralesional therapies, and radiotherapy, there is still no universally recognized safe and effective method. Previous studies have suggested that transcatheter arterial infusion (TAI), as a locoregional therapeutic strategy, may enhance the management of local lesions through targeted drug delivery. However, the existing literature on the efficacy and safety of TAI utilizing immune checkpoint inhibitors (ICIs) is limited. The aim of this study was to assess the efficacy and safety of TAI of ICIs in patients diagnosed with AM, as well as to investigate clinical factors that may affect treatment outcomes. **Methods:** This study involved a retrospective analysis of patients with AM who underwent TAI of ICIs across multiple centers. Participants received TAI of PD-1 inhibitors or a combination of PD-1 and CTLA-4 inhibitors every three weeks, in conjunction with systemic therapy. The primary endpoint was the objective response rate (ORR), while secondary endpoints included the disease control rate (DCR), progression-free survival (PFS) of locoregional lesions, duration of response (DoR), and overall survival (OS). **Results:** A total of 44 patients with AM were enrolled and analyzed between May 2019 and January 2025. All participants had received at least two TAI treatments and had at least one evaluable locoregional lesion in the extremities, as determined by enhanced MRI or CT imaging. The cohort consisted of 23 females (52%) and 21 males (48%), with a median follow-up period of 10.6 months. The overall ORR was 36.4%, and the DCR was 86.4%. The ORR and DoR for lesions treated with TAI were 40.9% and 90.1%, respectively. Five patients (11%) achieved a complete response (CR), one of whom demonstrated a pathological complete response. The median DoR and OS were recorded at 11.8 months and 32.2 months, respectively. First-line treatment exhibited a significantly higher ORR (82.4% vs. 14.8%, $P < .001$) and longer PFS (24.9 months vs. 3.5 months, $P < .001$) compared to subsequent-line treatments. Adverse events were primarily classified as grade 1-2, with no instances of grade 4-5 events, and there were no treatment-related discontinuations or fatalities. **Conclusions:** This study provides evidence for the safety of TAI of ICIs and suggests that it may represent an effective first-line treatment option for Chinese patients with locoregional unresectable lesions of AM, demonstrating significant local control efficacy in real-world clinical settings. Research Sponsor: None.

9547 Poster Session

The phase 1 clinical trial of anti–PD-1 ab plus intrahepatic injection of oncolytic virus (OH2) combined radiotherapy of liver metastasis in stage IV melanoma.

Xuan Wang, Chuanliang Cui, Hongzhi Wang, Shanshan Yin, Yue Cong, Hui Tian, Bin Lian, Jiayi Yu, Lu Si, Zhihong Chi, Xinan Sheng, Yan Kong, Caili Li, Lili Mao, Li Zhou, Siming Li, Jie Dai, Xiaoting Wei, Weihu Wang, Jun Guo; Department of Melanoma and Sarcoma, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Haidian District, China; 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 Radiation Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Department of Ultrasound, Peking University Cancer Hospital & Institute, Beijing, China; Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China; Peking University Cancer Hospital & Institute, Beijing, China; Department of Radiation Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Department of Melanoma and Sarcoma, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Melanoma and Sarcoma, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Radiation oncology, Peking University Cancer Hospital & Institute, Beijing, China; Peking University Cancer Hospital and Institute, Beijing, China

Background: Patients with melanoma and liver metastases generally exhibit reduced responses to systemic immunotherapy. Oncolytic herpes simplex virus 2 (OH2), is an oncolytic virus with potential therapeutic benefits. Preliminary clinical trials have demonstrated the efficacy of combining PD-1 antibody therapy with intrahepatic intralesional injections of OH2. Additionally, liver metastasis radiotherapy may modulate the tumor microenvironment, potentially enhancing the efficacy of immunotherapy combinations. In this phase I study, we aim to evaluate the safety and efficacy of OH2 and Pucotenlimab, in combination with liver metastasis-directed radiotherapy in patients with melanoma. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extra-hepatic metastasis; the ocular melanoma and brain metastasis were excluded. Pts received intravenous Pucotenlimab Q3W combined with ultrasound guided intrahepatic injection of OH2 Q2W (10^7CCID50/mL, 8ml per injection) after SBRT (24-30Gy/3Fx) of liver metastasis. The primary endpoint was ORR. Clinical trial: NCT05068453. **Results:** From Dec 2021 to Jan 2025, 20 pts were enrolled. 77.8% had received at least one prior treatment; 52.9% presented with extrahepatic metastases. The median size of enrolled lesions was 34.56 mm (13.0–271.0 mm). The median number of liver metastases was 5.5. Among these patients, 17 were evaluable for efficacy. One iCR, four iPR, resulting in an ORR of 29.4% and a DCR of 52.9%. Nearly 60.0% of pts exhibited a reduction in target lesions, including 65.2% of intrahepatic lesions, and 41.7% of extrahepatic lesions with a maximum reduction of 100.0%. Among injection target lesions, 58.3% demonstrated shrinkage,. In non-injection target lesions, 54.5% exhibited shrinkage. The median follow-up was 17.0m. The 1-year survival rate observed was 60.0%, while the 2-year was 51.4%. The OS has not been reached. Interestingly, no clear correlation has been established between imaging evaluations and patient prognosis. Among the pts classified as having PD, 10 individuals continued treatment due to clinical benefits. Notably, their OS was comparable to that of the overall population, with 2-year survival rate 60.0%. No treatment-related deaths reported. Adverse events were minimal, with only two grade 3 TRAEs observed: pneumonia and colitis. Biopsies of 17 pts with injected lesions were analyzed 8 to 12 weeks after the first injection. Of these, five pts (1 iCR, 1 iPR, and 3 SD) showed no residual tumor cells, accompanied by TIL infiltration. All five pts exhibited long PFS. **Conclusions:** The combination of systemic anti-PD-1 therapy with intralesional injection of an oncolytic virus and radiotherapy has demonstrated a remarkable ORR and excellent OS in patients with melanoma and liver metastases, with manageable toxicity. Clinical trial information: NCT05068453. Research Sponsor: None.

9548 Poster Session

Influence of tumor infiltrating lymphocytes (TIL) monotherapy on persistent clinical and immunological responses in Asian metastatic melanoma patients with specific CD8+ TIL proportions: A phase I trial.

Chuanliang Cui, Li Zhou, Yan Kong, Xuan Wang, Zhihong Chi, Fenge Li, Lu Si, Bin Lian, Lili Mao, Yue Yang, Hui Tian, Bixia Tang, Siming Li, Yongming Xue, Xiaoqing Zhang, Zhenya Zhu, 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; Department of Melanoma and Sarcoma, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Melanoma and Sarcoma, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Haidian District, China; Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China; Suzhou Blue Horse Medical Technology Co., Ltd, Suzhou, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China; Peking University Cancer Hospital & Institute, Beijing, China; Department of Melanoma and Sarcoma, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Genitourinary Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Beijing Cancer Center, Beijing, China

Background: TIL therapy, as one of the most promising adaptive cellular immunotherapy, has shown success in metastatic melanoma, with a median overall response rate (ORR) of 28% and median PFS (progression free survival) of 7.2 months. This phase I clinical trial aimed to explore the safety, feasibility, and efficacy of TILs monotherapy in Asian metastatic melanoma pts. **Methods:** Pts with metastatic melanoma who had progressed on standard therapies, had both resectable and measurable tumors were eligible to be enrolled. Pts received a lymphodepletion regimen which consisted of cyclophosphamide (30mg/kg) for 2 days, followed by Fludarabine (25mg/m^2) for 5 days, approximately 24 hours before receiving the intravenous autologous LM103 (TILs) infusion and then high dose IL-2 for 6 doses (200000IU/Kg, 1 dose per day. Doses can be adjusted based on pts tolerance to support T cell survival and proliferation. **Results:** Twelve pts (aged 26-68 yrs) with metastatic melanoma were enrolled and treated, including 8 males. Among the primary melanoma types, 6 were acral, 3 mucosal, 2 unknown, and 1 cutaneous. 7 pts had distant organ metastases. As of Jan 2025, 8 out of 12 pts were assessable, one could not be evaluated due to rapid brain metastases and 3 remained under safety observation (median follow-up, 6 wks; range, 2-48 wks). Resected tumors used for TIL production were from 8 metastatic lymph nodes and 4 subcutaneous nodules. The infused autologous TIL contained 8.24-19.47X10^{10} viable cells. The median duration of IL-2 infusion were 5.08 days, with a median dose of 13.75 IU/Kg/day. The most frequent treatment-emergent adverse events (TEAEs) were myelosuppression (100%), fever (100%), anemia (100%), and hypotension (100%). Grade 3-4 TEAEs included neutropenia (100%), lymphopenia (100%), leukopenia (100%), fever (75%), thrombocytopenia (62.5%), and anemia. The ORR was 50% (4/8, 4PR, 2SD, 2PD) per RECIST v1.1. The median PFS was not reached and the longest PFS was 11.4 months. Responders demonstrated a larger number of T cell clones, higher T cell receptor (TCR) diversity (Inverse Simpson Index), and lower TCR clonality compared to non-responders (P=0.031,P=0.049 and P=0.033), based on real time peripheral monocytes analysis. These findings suggest that the LM103 in responders recognized a broader antigen spectrum. Notably, about 50% of initial TCR clones can be detected 18 wks post-infusion, suggesting LM103 persistence. Post-hoc analysis revealed that responders had a CD8+ T-cells proportion of 60-80%, while non-responders exhibited extreme proportions (<10% or >80%). **Conclusions:** LM103 was well tolerated and demonstrated durable responses in Asian patients with advanced melanoma. Patients with 60-80% CD8+T-cell proportions are more likely to respond to TIL therapy. Clinical trial information: CTR20233999. Research Sponsor: None.

9549 Poster Session

Intensive surveillance and aggressive multi-modal treatment for liver metastases from uveal melanoma.

Hemant M. Kocher, Mohammed Akil Gani, Mandeep S. Sagoo, Peter Wojciech Szlosarek, Amina Saad, Ziya Belibagli, Karen Mawire, The London Clinic and Barts & the London HPB MDT and Ocular Oncology MDT; Queen Mary University of London, London, United Kingdom; The London Clinic, London, United Kingdom; Moorfields Eye Hospital, London, United Kingdom; Barts Cancer Institute, London, United Kingdom; Barts Health NHS Trust, London, United Kingdom

Background: We report utility of diagnostic laparoscopy and long-term survival outcome for patients undergoing multi-modal treatment for liver metastasis from uveal melanoma (LMUM). **Methods:** All consecutive patients with suspected oligo-metastatic LMUM diagnosed on screening ultrasound were discussed at Hepato-Pancreatico-Biliary (HPB) Tumour Boards (Jan2010-Nov2024) and were offered multiple lines of surgical / ablation, liver directed and systemic therapies as appropriate, with data censored on 30th November 2024. Liver specific overall survival was calculated from date of index liver resection to date of last follow-up (censored) or death. **Results:** Out of the 58 patients LMUM, 13 (22%) patients had multifocal disease or other concurrent cancer diagnosed on further imaging assessments (dedicated MRI liver and FDG-PET scan). Of the remaining 45 patients assessed with diagnostic laparoscopy a further 15 (33%) had multifocal hepatic metastasis. Thus 27 patients (46%) had multifocal disease precluding liver resection / ablation (Group A). 21 of 58 patients with LMUM had liver resection as a primary modality with majority (18/21) achieving a R0 resection margin and a further 10 had liver ablation (Group B). Both groups received additional lines of treatment. Patients with oligo-metastatic disease undergoing liver resection / ablation as primary modality of treatment (Group B) had longer overall survival (median liver-specific OS = 45.1 (95% CI: 31 – not reached) months; $p<0.0001$, log-rank (Mantel-Cox) test, Hazard ratio (HR): 7.86, 95%CI: 3.52-17.5) after treatment of metastatic disease compared to multi-focal disease treated with immunotherapy as primary modality (Group A, median 18.6 (95% CI: 13-26) months). Whilst the age of diagnosis of LMUM was similar for both Groups A (multifocal metastasis, median 68 years) and B (oligometastatic disease, median 63 years) (two-tailed Mann Whitney U test, $p=0.12$), patients group B were younger at time of diagnosis of primary UM (median 57 (B) versus median 66 years (A), two tailed Mann Whitney U test, $p=0.03$) with a longer interval to metastatic progression (median 1325 days (B) versus median 704 days (A), two tailed Mann Whitney U test, $p=0.006$). **Conclusions:** This largest series of patients with LMUM from the United Kingdom emphasises the vital role of diagnostic laparoscopy to rule out bi-lobar miliary disease. We report impactful overall survival with multimodal treatment for LMUM and highlight prognostic features for further validation. Research Sponsor: The London Clinic.

High-dose 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) chemoembolization for treatment-naïve patients with limited uveal melanoma hepatic metastases.

Carin F. Gonsalves, Robert D. Adamo, Nolan John Boon, Carolyn Palumbo, Rino S. Seedor, Marlana M. Orloff, Takami Sato, David J. Eschelman; Sidney Kimmel Comprehensive Cancer Center, Thomas Jefferson University, Philadelphia, PA; Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University, Philadelphia, PA

Background: Nearly 50% of patients with uveal melanoma (UM) develop metastases with the liver being the primary site of disease in > 90% of cases. Control of hepatic tumors is crucial to prolonging overall survival (OS) for metastatic uveal melanoma (MUM) patients. We report results of aPhase II prospective trial [NCT04728633] using high-dose BCNU chemoembolization (TACE) as first-line treatment for limited UM hepatic metastases. **Methods:** MUM patients with < 50% hepatic tumor burden and no significant extrahepatic disease were treated with hepatic artery infusion of 300mg of BCNU diluted in ethiodized oil followed by gelatin sponge embolization until maximum clinical benefit, hepatic and/or extrahepatic disease progression (PD), or development of significant adverse events (AE). Tumor response (RECIST 1.1) was assessed using CT and MRI. Treatment breaks were allowed for patients with disease control (partial response [PR] + stable disease [SD]) to reduce toxicities and optimize quality of life. Retreatment with TACE was permitted if PD occurred during treatment breaks. OS, progression-free survival from liver (PFS-L) and systemic metastases were analyzed. Toxicities were assessed using CTCAE v5.0. **Results:** Twenty-eight patients (17 men; median age, 62; range, 39 - 84) were enrolled from October 2021 to January 2025. Bilobar (n=25) or unilobar (n=3) BCNU TACE was performed every 4 or 7 weeks (+/- 7 days), respectively. Median follow-up was 11.6 months (range, 1.8 – 37.6). Median OS was 14.1 months (range, 1.8 – 37.6) with 13 surviving patients. Best treatment response included PR in 8, SD in 18, and PD in 2 patients for an overall response rate of 28.6% and a disease control rate of 92.9%. Twenty-two (78.6%) patients with disease control had treatment breaks. One patient withdrew from the trial to pursue percutaneous hepatic perfusion despite SD for 25 months. Median PFS-L was 9.9 months (range, 1.8 – 36.8). Sixteen (57.1%) patients developed new/nontarget hepatic tumor progression (n=13) or progression of target and nontarget lesions (n=3). Treatment-related grade 3 AEs included pain (n=5), hypertension (n=4), incidental pulmonary emboli (n=3), thrombocytopenia (n=1) and an infected biloma. Self-limiting grade 3 or 4 liver enzyme elevation occurred in 6 patients. Fifteen (53.6%) patients developed extrahepatic disease (median, 7.3 months); 11 patients (7 with stable liver tumors) started systemic therapy off-trial. Three patients developed life-limiting AEs due to checkpoint inhibitor therapy. **Conclusions:** High-dose BCNU TACE provided disease control in the majority of treatment-naïve patients with limited UM hepatic metastases. PD typically occurred during treatment breaks, as expected. Future trials exploring the combination of BCNU TACE with systemic therapies to address both hepatic and extrahepatic metastases are warranted. Clinical trial information: NCT04728633. Research Sponsor: Guerbet.

Gotistobart in combination with pembrolizumab in patients with advanced melanoma who have progressed on PD-1 inhibitors with or without CTLA-4 inhibitors.

Siwen Hu-Lieskovan, Kari Lynn Kendra, Kai He, Bently Patrick Doonan, Eric S. Schaefer, Edward Arrowsmith, Ki Young Chung, Eric D. Whitman, Ulka N. Vaishampayan, Svetlana Shpyro, Qiong Wang, Juanjuan Su, Chris Leung, Kazuharu Kai, Yang Liu, Pan Zheng, Tianhong Li; University of Utah Health, Salt Lake City, UT; The Ohio State University, Columbus, OH; University of Florida College of Medicine, Gainesville, FL; Highlands Oncology Group, Fayetteville, AR; Tennessee Oncology, Chattanooga, TN; PRISMA Health Cancer Institute, Institute for Translational Oncology Research, Boiling Springs, SC; Atlantic Health System, Morristown, NJ; Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; BioNTech SE, Mainz, Germany; OncoC4 Inc, Rockville, MD; OncoC4, Rockville, MD; OncoC4, Inc., Rockville, MD; UC Davis Comprehensive Cancer Center, Sacramento, CA

Background: Patients with advanced melanoma who progress on PD-1 and CTLA-4 inhibitors (IO-R/R) have poor prognosis. Gotistobart is a pH-sensitive anti-CTLA-4 mAb and we hypothesized that gotistobart in combination with pembrolizumab (pembro) could improve outcomes for ipilimumab plus nivolumab (ipi/nivo) treatment failure. PRESERVE-001 (NCT04140526) is a phase 1/2 study that evaluates safety and efficacy of gotistobart with pembro in patients with IO-R/R advanced melanoma. **Methods:** Patients with IO-R/R advanced melanoma were treated with 3 mg/kg or 6 mg/kg gotistobart plus 200 mg of pembro, Q3W. Treatment beyond progression was allowed at the physician's discretion. Primary endpoints were ORR (RECIST 1.1) and safety. Exploratory endpoints included OS and an ad-hoc analysis of next-treatment free survival (NTFS; next treatment was identified as initiation of a new antineoplastic agent). **Results:** As of December 19, 2024, 33 and 34 patients received 3 mg/kg and 6 mg/kg gotistobart plus pembro, with median follow up associated with OS of 14.7 and 10.7 months, respectively. Of these, 67% (22/33) and 68% (23/34) had progressed on ipi/nivo. 30% (20/67) had tumors ≥10cm at study entry. Unconfirmed ORR (uORR) was 25.0% (8/32) and 26.5% (9/34), respectively, with 2 patients achieving CR in the 6 mg/kg group. Of patients who had prior ipi/nivo, uORR was 23.8% (5/21) and 21.7% (5/23), respectively. Efficacy was noted regardless of BRAF mutation status. NTFS rates at 12 months were 45.3% (95% CI 26.0–62.7) and 38.5% (95% CI 20.3–56.4), respectively. OS rates at 18 months were 61.7% (95% CI 40.1–77.5) and 51.9% (29.3–70.4), respectively. Grade ≥ 3 TRAEs were observed in 51.5% and 61.8% of patients in the 3 mg/kg and 6 mg/kg groups, respectively, with colitis/diarrhea or AST/ALT increase being most common. 30.3% and 32.4% of patients, respectively, were able to continue treatment after dose reduction. **Conclusions:** Gotistobart 3 mg/kg or 6 mg/kg plus pembro 200 mg, Q3W, provided durable response and clinically meaningful OS benefit, regardless of prior ipi treatment, with nearly half of patients being next-treatment free at one year follow up. To our knowledge,this is one of the largest cohorts ever studied in patients with advanced melanoma R/R to ipi/nivo. Clinical trial information: NCT04140526. Research Sponsor: OncoC4 Inc; BioNTech SE; SBIR; R44CA250884; National Cancer Institute.

Additional parameters	Gotistobart 3 mg/kg (N = 33)	Gotistobart 6 mg/kg (N=34)
Median age (range)	62 (29–83)	66 (24–81)
Female n (%)/Male n (%))	12 (36%)/21 (64%)	12 (35%)/22 (65%)
ECOG score = 1 (of 0 or 1)	18 (55%)	16 (47%)
Prior treated with ipi/nivo	22 (67%)	23 (68%)
Gotistobart treatment duration in weeks, median (range)	19.0 (3–96)	8.9 (3–130)
uORR % (n)	25.0% (8/32)	26.5% (9/34)
uORR in patients prior treated with ipi/nivo % (n)	23.8% (5/21)	21.7 (5/23)
DCR % (95% CI)	50 (31.9, 68.1)	50 (32.4, 67, 6)
NTFS rates at 12 months % (95% CI)	45.3 (26.0, 62.7)	38.5 (20.3, 56.4)
OS rate at 18 months % (95% CI)	61.7 (40.1–77.5)	51.9 (29.3–70.4)

9552 Poster Session

Nautilus, a phase 1b/2 trial of combining oral HDAC inhibitor (HDACi) with MEK inhibitor (MEKi) in patients with NRAS-mutated metastatic melanoma (MM).

Rodabe Navroze Amaria, Herbert Leon Duvivier, Katy K. Tsai, Parisa Momtaz, Robert W. Galamaga, Evan P. Pisick, Bently Patrick Doonan, Amy M. Weise, Natalie Langr, James D. Winkler, Harish P. Dave, Jennifer Robinson Diamond, Ryan J. Sullivan; The University of Texas MD Anderson Cancer Center, Melanoma Medical Oncology, Houston, TX; City of Hope Atlanta, Newnan, GA; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; Memorial Sloan Kettering Cancer Center, New York, NY; City of Hope Phoenix, Goodyear, AZ; City of Hope - Chicago, Zion, IL; University of Florida College of Medicine, Gainesville, FL; Henry Ford Cancer Hospital, Detroit, MI; OnKure, Inc., Boulder, CO; OncoBay Clinical, Raleigh, NC; Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO; Massachusetts General Hospital Cancer Center, Boston, MA

Background: Activating NRAS mutations occur in 15-20% of MM cases. The MEK inhibitor binimetinib has modest single agent activity with 15% objective response rate (ORR) and 2.8 month progression-free survival (PFS). Bocodepsin (OKI-179) is a novel Class I-selective, oral histone deacetylase inhibitor that was found to have synergistic efficacy with MEKi in preclinical models of NRAS-mutated melanoma. Cells displayed unrepaired double strand DNA breaks and cellular apoptosis, while regressions were observed in xenograft models. Here we present the results of the phase 2 portion of a clinical trial of this combination in NRAS-mutant MM (NCT05340621). **Methods:** In this Phase 2 study, only patients with NRAS-mutant MM previously treated with immunotherapy were enrolled and treated with bocodepsin at the recommended phase 2 dose (300 mg daily, 4 days on, 3 days off, continuously) with binimetinib (45 mg twice daily, continuously). Primary endpoint was ORR, with secondary endpoints including safety and PK analyses. **Results:** As of 1/3/2025, 36 total patients were enrolled; 14 in phase 1b dose escalation and 22 in phase 2, including a total of 24 NRAS-mutant melanoma patients. Median age of NRAS-mutant MM patients was 69 years, and 47% of patients were males. Median numbers of prior therapies was 3 and LDH elevations were found in 41% of patients. There were no grade 3/4 toxicities seen in >10% of patients, including no episodes of high grade rash. Of the 20 evaluable patients with NRAS-mutant MM, ORR was 30%. The median PFS was 7.25 months (5-92 weeks). **Conclusions:** The combination of bocodepsin and binimetinib in patients with NRAS-mutant melanoma is tolerable with manageable AEs and no high grade rash. Initial response data in patients with NRAS-mutant melanoma are supportive of potential combinatorial activity of a MEK inhibitor and HDACi bocodepsin. Further investigation is crucial as MM patients with disease progression after immunotherapy remain in need of rational therapeutic options. Thus, MEKi + HDACi warrants further study in a larger patient cohort. Clinical trial information: NCT05340621. Research Sponsor: OnKure.

9553 Poster Session

First-line lenvatinib plus pembrolizumab versus placebo plus pembrolizumab in Chinese patients with unresectable or metastatic melanoma: Results from LEAP-003.

Jun Guo, Xiaoshi Zhang, Di Wu, Lu Si, Ya Ding, Zhiguo Luo, Xiubao Ren, Zhengyun Zou, Yu Chen, Meiyu Fang, Ke Li, Quanli Gao, Hongming Pan, Chinyere E Okpara, Wei Wang, Shanshan Chen, Mizuho Fukunaga-Kalabis, Ana Maria Arance; Beijing Cancer Hospital, Beijing, China; Sun Yat-sen University Cancer Centre, Guangzhou, China; The First Hospital of Jilin University, Changchun, China; Fudan University Shanghai Cancer Center, Shanghai, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Nanjing Drum Tower Hospital, Jiangsu, China; Fujian Cancer Center, Fujian, China; Zhejiang Cancer Hospital, Hangzhou, China; Yunnan Cancer Hospital, Kunming, China; Henan Cancer Hospital, Zhengzhou, China; Sir Run Run Shaw Hospital, Hangzhou, China; Eisai Ltd., Hatfield, United Kingdom; MSD China, Beijing, China; MSD China, Shanghai, China; Merck & Co., Inc., Rahway, NJ; Hospital Clinic Barcelona and IDIBAPS, Barcelona, Spain

Background: Results of the global, phase 3 LEAP-003 study, showed that lenvatinib (len) + pembrolizumab (pembro) significantly improved PFS compared with pembro alone in participants (pts) with predominantly cutaneous melanoma at the first interim analysis, but this benefit was not maintained with additional follow-up and there was no improvement in OS. Previous studies have shown that mucosal and acral melanomas, which are the predominant subtypes in Chinese patients, may benefit from combination therapy. Here, we present results for Chinese participants (pts) enrolled in the LEAP-003 global (NCT03820986) and China extension (NCT04889118) studies. **Methods:** Eligible pts were aged ≥18 y, had previously untreated unresectable stage III or IV melanoma, an ECOG PS of 0 or 1, and measurable disease per RECIST v1.1. Pts were randomly assigned 1:1 to len 20 mg or placebo (pbo) PO QD + pembro 200 mg IV Q3W for ≤2 y. Dual primary end points were PFS per RECIST v1.1 by BICR and OS. Secondary end points were ORR, DOR, and safety. **Results:** 131 pts from China enrolled and received treatment (len + pembro, n = 64; pbo + pembro, n = 67). Median time from first dose to data cutoff (Jan 18, 2023) was 18.1 mo (range, 12.7-29.5). In the overall China subgroup, median PFS was 6.1 mo (95% CI, 4.1-8.1) for len + pembro vs 2.0 mo (95% CI, 2.0-2.1) for pbo + pembro (HR, 0.55; 95% CI, 0.37-0.81); 18-mo PFS was 20.0% vs 12.8%. Median OS was 19.9 mo (95% CI, 11.9-26.8) for len + pembro vs 17.0 mo (95% CI, 12.7-25.7) for pbo + pembro (HR, 0.93; 95% CI, 0.58-1.48); 18-mo OS was 53.4% vs 49.6%. ORR was 26.6% (95% CI, 16.3-39.1; 4 CR, 13 PR) for len + pembro vs 16.4% (95% CI, 8.5-27.5; 4 CR, 7 PR) for pbo + pembro; median DOR was 13.7 mo (range, 3.8-21.4) vs NR (range, 4.2-21.4+). Among 30 pts with mucosal melanoma, median PFS was 8.1 mo (95% CI, 5.9-12.4) for len + pembro (n = 16) vs 2.0 mo (95% CI, 1.9-4.1) for pbo + pembro (n = 14; HR, 0.44; 95% CI, 0.20-0.97); 12-mo PFS was 33.5% vs 21.4%. Median OS was 26.8 mo (95% CI, 10.6-NR) for len + pembro vs 14.3 mo (95% CI, 9.0-NR) for pbo + pembro (HR, 0.51; 95% CI, 0.17-1.55); 18-mo OS was 68.8% vs 49.0%. ORR among pts with mucosal melanoma was 50.0% (95% CI, 24.7-75.3; 1 CR, 7 PR) for len + pembro vs 7.1% (95% CI, 0.2-33.9; 1 PR) for pbo + pembro. Treatment-related AEs occurred in 96.9% in the len + pembro arm vs 97.0% in the pbo + pembro arm (grade 3-5: 62.5% vs 16.4%). One pt (1.5%) in the pbo + pembro arm died due to treatment-related immune-mediated lung disease. **Conclusions:** In Chinese pts, the efficacy and safety profile observed with len plus pembro vs pembro alone was consistent with the global population. Numerical improvements in PFS and ORR in the mucosal melanoma subtype treated with len + pembro were notable, although the data should be interpreted with caution due to the limited sample size. These results support first-line pembro monotherapy as a standard-of-care for this population. Clinical trial information: NCT03820986, NCT04889118. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and Eisai Inc., Nutley, NJ, USA.

9554 Poster Session

Efficacy and safety of first-line (1L) nivolumab plus relatlimab (NIVO + RELA) versus NIVO plus ipilimumab (NIVO + IPI) in advanced melanoma: An updated indirect treatment comparison (ITC) with 4-year follow-up data.

Dirk Schadendorf, Hussein A. Tawbi, Evan J. Lipson, F. Stephen Hodi, Paolo Antonio Ascierto, James Larkin, Christopher D. Lao, Caroline Gaudy-Marqueste, Jennell Palaia, Viviana Garcia Horton, Zheng-Yi Zhou, Dana Christensen, Hannah H Kim, Andriy Moshyk, David R. D'Adamo, Abraham Selvan, Divya Patel, Leon A. Sakkal, Georgina V. Long; University of Essen and the German Cancer Consortium, Essen, Germany; The University of Texas MD Anderson Cancer Center, Houston, TX; Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Massachusetts General Hospital, Boston, MA; Instituto Nazionale Tumori IRCCS – Fondazione Pascale, Naples, Italy; Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; University of Michigan, Ann Arbor, MI; Aix-Marseille University, Marseille, France; Bristol Myers Squibb, Princeton, NJ; Analysis Group, Inc., Boston, MA; Bristol-Myers Squibb Co, Lawrenceville, NJ; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia

Background: An ITC comparing NIVO + RELA and NIVO + IPI, approved dual immunotherapy treatment options for patients (pts) with advanced melanoma, was previously conducted using pt-level data from the pivotal RELATIVITY-047 (RELA-047; NIVO + RELA vs NIVO) and CheckMate 067 (CM-067; NIVO + IPI or NIVO vs IPI) trials (Long JCO 2024). Here we present updated results using 4-year follow-up data from RELA-047. **Methods:** Inverse probability of treatment weighting was used to adjust for cross-trial imbalances in baseline characteristics. CM-067 follow-up was truncated (median 41.0 mo) to best align with the follow-up length in RELA-047 (median 34.9 mo). Progression-free survival (PFS) per investigator, confirmed objective response rates (ORRs) per investigator, overall survival (OS), and melanoma-specific survival (MSS) were analyzed. Outcomes were also evaluated across key subgroups. The weighted NIVO arms from each trial were compared for internal validation. **Results:** After weighting, key baseline characteristics were balanced for NIVO + RELA (n=339) and NIVO + IPI (n=297). Outcomes after weighting were similar between NIVO + RELA and NIVO + IPI (hazard ratio [HR] [95% CI]: PFS 1.08 [0.89–1.33]; OS 0.95 [0.76–1.19]; table). Outcomes were similar between the NIVO arms, validating the ITC methodology. Across subgroups, efficacy appeared similar between treatments, although trends favoring NIVO + IPI were observed for ORR among pts with BRAF-mutant disease or serum lactate dehydrogenase >2x the upper limit of normal. Results when NIVO + IPI follow-up was untruncated were consistent with the truncated analyses. **Conclusions:** Consistent with previous results, this updated ITC with longer follow-up from RELA-047 suggests that 1L treatment with NIVO + RELA may have comparable efficacy to NIVO + IPI in pts with advanced melanoma, including most—but not all—subgroups. Results should be interpreted with caution given differences in study design and changes in the treatment landscape over time. Research Sponsor: Bristol Myers Squibb.

Efficacy outcomes after weighting.

	NIVO + RELA (n = 339)	NIVO + IPI (n = 297)	HR/odds ratio [OR] (95% CI)	NIVO RELA-047 (n = 338)	NIVO CM-067 (n = 288)	HR/OR (95% CI)
Median PFS per INV, mo (95% CI)	12.0 (8.2–17.1)	11.2 (8.5–18.1)	1.08 (0.89–1.33)	6.6 (4.6–10.1)	5.7 (3.9–9.1)	0.96 (0.79–1.16)
Confirmed ORR per INV, %	48	50	0.91 (0.73–1.14)	40	40	1.00 (0.79–1.28)
Median OS, mo (95% CI)	64.5 (38.6–NR)	NR (37.1–NR)	0.95 (0.76–1.19)	35.1 (27.3–48.8)	35.7 (26.4–NR)	1.02 (0.83–1.26)
Median MSS, mo (95% CI)	NR (NR–NR)	NR (NR–NR)	0.87 (0.68–1.12)	51.2 (34.7–NR)	44.8 (32.3–NR)	0.96 (0.76–1.21)

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

9555 Poster Session

Phase 2 study of axitinib + nivolumab in mucosal melanoma with pilot addition of stereotactic body radiotherapy or ipilimumab in select progressors.

Sarah E. Lochrin, Hannah L. Kalvin, Monica F. Chen, James William Smithy, Parisa Momtaz, Michael A. Postow, Shirlanna Station, Amanda J. Hill, Charlene Garcia Hochreiter, Roseann Durak, Katherine Panageas, Randy Yeh, Christopher A. Barker, Alexander Noor Shoushtari; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

Background: Mucosal melanoma (MM) is an aggressive subtype of melanoma with distinct biology, and outcomes in advanced disease are inferior compared with cutaneous melanoma. Frontline Chinese studies in MM have shown efficacy of combined VEGF/R and PD-1 blockade, but studies in more diverse populations and options in PD-1 resistance are lacking. **Methods:** We conducted a phase 2/1b single-center trial in patients (pts) with untreated, unresectable or advanced MM. Pts received standard nivolumab (nivo) plus axitinib (axi) 5mg PO twice daily. Primary endpoint of the phase 2 doublet arm was objective response rate (ORR) by RECIST 1.1 (H0=23%, Ha=48%). Clinical benefit rate (CBR) was defined as ORR or stable disease (SD) >6 months (mos). Upon progression with good tolerance, the phase 1b triplet arm pts received the addition of either stereotactic body radiotherapy (SBRT, 30Gy/5 fractions) or ipilimumab (ipi, 1mg/kg < 4 doses) to ongoing nivo + axi. The primary endpoint of the triplet was safety by CTCAE v5.0 and adverse events (AEs) of special interest (AESIs). Kaplan-Meier methods estimated time to event outcomes; ORR and AEs were reported as proportions with exact 95% confidence intervals. **Results:** N=21 pts were enrolled; N=20 were evaluable for efficacy. See Table for baseline population characteristics. Median follow up was 15 mos (IQR 6, 21), 45% of pts (95% CI: 23, 68) had an objective response; 3 complete and 6 partial responses. Median duration of response was 13 mos (8.6, not reached (NR)). SD persisted ≥ 6 mos in 2 of 7 pts; CBR was 55% (95% CI: 32,77). Median progression free survival (PFS) was 6.3 mos (3.5, NR), and 12-mos estimated PFS and overall survival was 37% (20,67) and 71% (52, 96), respectively. Rate of grade ≥3 treatment related AEs (TRAE) in the doublet arm (n=21) was 67% (95% CI: 43,85), most commonly hypertension & hepatitis, with two pt deaths; 1 nivo-related myasthenia gravis / myositis, and 1 nivo-related pancreatitis with steroid-related PJP pneumonia. 14 pts (70%) progressed on doublet therapy, of which 7 enrolled on the triplet arm. N=5 received ipi and N=2 SBRT (both to anorectal primaries and adjacent lymph nodes). There were 2 grade ≥3 TRAEs in the ipi triplet arm (hepatitis), 0 in the SBRT arm, no grade 5 events, and no AESIs. Zero of 4 evaluable pts in ipi triplet and 1 of 2 in the SBRT triplet responded (4+ mos, ongoing). **Conclusions:** The frontline combination of nivolumab and axitinib was effective in patients with unresectable or advanced outside of China, and a prospective global study randomized against immune checkpoint blockade is warranted. Adding either ipi or SBRT to nivo-axi appears safe in select pts with progressive disease and further studies are needed for pts with PD-1 resistant MM. Clinical trial information: NCT05384496. Research Sponsor: National Comprehensive Cancer Network (NCCN); Pfizer.

Characteristic (n=21)	N (%)
Age (median)	73 years (IQR: 67, 82)
Sex	
Female	13 (62%)
Male	8 (38%)
Race	
Caucasian	16 (76%)
Asian	3 (14%)
Black	2 (10%)
Primary Site	
Anorectal	10 (48%)
Sinonasal	8 (38%)
Vulvovaginal	3 (14%)
Stage	
Locoregionally advanced	14 (67%)
Metastatic	7 (33%)
LDH (median)	195 (IQR: 171,201)

Phase I dose escalation trial of STX-001, an LNP-encapsulated self-replicating mRNA expressing IL-12, in patients (pts) with advanced solid tumors.

Sarina A. Piha-Paul, Kamalesh K Sankhala, Alexander M. Menzies, Madhuri Dey, Julian Quiñones, Ryan T. Sowell, Prashant Nambiar, Robert Shine, Katherine Kacena, Shari Thomas, LeeAnn Ali, Neil Sankar, Tasuku Kitada, Jason J. Luke, Georgina V. Long; The University of Texas MD Anderson Cancer Center, Houston, TX; Precision NextGen Oncology, Beverly Hills, CA; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Strand Therapeutics Inc., Boston, MA; UPMC Hillman Cancer Center, Pittsburgh, PA; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia

Background: STX-001 is a lipid nanoparticle-encapsulated self-replicating mRNA that activates innate immunity, promotes immunogenic cancer cell death, and expresses IL-12 to induce immune responses against tumors. Preclinical models demonstrated significant immune modulation and antitumor activity. **Methods:** Eligible pts had treatment-refractory advanced solid tumors with ≥ 1 clinically injectable lesions. Bayesian Optimal Interval design was used with an initial 3 + 3 run-in for dose escalation. STX-001 was administered intratumorally every 3 weeks. Dose-limiting toxicities (DLTs) were assessed during the first treatment cycle and response was evaluated by RECIST 1.1. **Results:** From May 29, 2024 to data cutoff (Dec 16, 2024), 14 pts were enrolled across four dose levels (30 - 900 μg). Common Gr ≥ 3 treatment-related adverse events, which included transient neutropenia (4 pts; 29%), lymphopenia (3 pts; 21%), ALT increase (2 pts; 14%), and AST increase (2 pts; 14%), were largely acute and self-limiting, and allowed ongoing dosing. There was no febrile neutropenia or drug-induced liver injury. One pt in the 900 μg cohort experienced DLTs (Gr 3 cytokine release syndrome and Gr 4 lymphopenia) but remained on study. IL-12 expression and robust IFN-γ induction were observed in the plasma. Tumor biopsies showed robust increases in PD-L1 and CD4/CD8 T cell staining post-treatment in both injected and non-injected lesions compared to baseline. 7 pts had undergone on-treatment disease assessment. 5 out of 7 pts had melanoma and were all refractory to PD-1 + CTLA-4 or LAG-3 inhibitors. 3 out of 5 melanoma pts had shrinkage of non-injected lesions (abscopal effects) including one with a confirmed RECIST complete response (CR; 100 μg cohort; prior treatments: PD-1 + LAG3, CTLA-4, and PD-1 inhibitors; metastases in skin and lymph nodes; subcutaneous lesion injected), one with a RECIST partial response (PR; 30 μg cohort; prior treatments: PD-1 + CTLA-4, PD-1, PD-1 + LAG3, and CTLA-4 inhibitors; metastases in skin, lung, and muscle; subcutaneous lesions injected), and one with 100% target lesion reduction with pronounced inflammatory response across multiple cutaneous/visceral lesions (30 μg cohort; prior treatments: PD-1 and CTLA-4 + PD-1 inhibitors; metastases in skin, lymph nodes, and lung; [sub]cutaneous lesions injected) and on-going clinical benefit (despite initial RECIST progression). ctDNA analysis, peripheral blood and tumor microenvironment profiling, PK, and other translational analyses are ongoing. **Conclusions:** STX-001 demonstrates promising preliminary efficacy, robust immune activation, and a favorable safety profile. These results support the continued development of STX-001 both as monotherapy and in combination with immune checkpoint inhibitors. Dose optimization is ongoing. Clinical trial information: NCT06249048. Clinical trial information: NCT06249048 Research Sponsor: None.

Outpatient treatment-related toxicity after hospital discharge among patients receiving lifileucel for advanced melanoma.

James William Smithy, Hannah L. Kalvin, Elizabeth Cathcart, Erin Walicki, Michael A. Postow, Jae H. Park, Charlotte Eielson Ariyan, Katherine Panageas, Alexander Noor Shoushtari; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

Background: While inpatient toxicity associated with tumor infiltrating lymphocyte (TIL) therapy and IL-2 administration is well characterized, risks facing patients after hospital discharge are less understood. Better characterization of outpatient adverse effects (AEs) could guide the optimal frequency and duration of follow up for this growing patient population. **Methods:** We conducted a retrospective analysis of all patients with advanced melanoma discharged from Memorial Sloan Kettering Cancer Center after receiving investigational or commercial lifileucel from October 2020 to October 2024. We reviewed incidence and timing of new Grade 3+ treatment-related AEs (TRAEs), blood product administration, and readmission among all patients from the time of hospital discharge to the time of the start of a subsequent systemic therapy or death. **Results:** Fifty-three patients successfully discharged after lifileucel administration were identified; patient demographics are included in Table 1. The median follow up time from discharge in survivors was 5 months (interquartile range (IQR): 3, 18). Two patients (4%) developed new Grade 3+ TRAEs following hospital discharge, including new Grade 3 neutropenia 73 days after discharge and new Grade 3 hypoxia 104 days from discharge. Hypoxia was secondary to pleural effusions that developed in the setting of renal thrombotic microangiopathy. Four patients (7.5%) were readmitted for TRAEs including cytopenias, dyspnea, and syncope while 7 patients (13%) were readmitted for melanoma progression. Readmissions occurred a median of 85 (IQR: 39, 128) days after lifileucel infusion and 69 days (IQR: 19, 98) after initial discharge. Twelve patients (23%) received at least one outpatient blood product transfusion, including packed red blood cells (PRBCs; 10 patients) and platelets (6 patients). Within 30 days of initial discharge, six patients (11%) received at least one PRBC transfusion and 3 patients (5.7%) received at least one platelet transfusion. The median number of transfused PRBC units was 2 (IQR: 1,4) and the median number of platelet transfusions was 4 (IQR: 2, 4). **Conclusions:** Rates of new severe toxicity and treatment-related readmissions were low among patients discharged post-lifileucel. About one in four patients required blood products after discharge. Identification of risk factors for the development of outpatient TRAEs may inform personalized care following lifileucel administration. Research Sponsor: None.

Patient demographics.

Characteristic		N = 53[1]
Age at TIL infusion		61 (42, 66)
Sex	Male	29 (55%)
	Female	24 (45%)
Melanoma subtype	Cutaneous	19 (36%)
	Uveal	9 (17%)
	Acral	8 (15%)
	Unknown primary	8 (15%)
	Mucosal	5 (9.4%)
	Other	4 (7.5%)
BRAF status	Mutated	13/51 (25%)
	Wild type	38/51 (75%)
Treatment setting	Investigational	45 (85%)
	Standard of care	8 (15%)

1. N (%); Median (interquartile range).

9558 Poster Session

Results of phase III clinical trial of novel biosimilar of pembrolizumab (RPH-075).

Ilya Pokataev, Konstantin Penkov, Lyudmila Zhukova, Daniil Stroyakovsky, Rashida Orlova, Marina Sekacheva, Igor Samoylenko, Ali Mudunov, Aleksandr Sobolev, Mikhail Fedyanin, Rustem Safin, Anastasia Mochalova, Irina Rozhkova, Ruslan Zukov, Vadim Kozlov, Vasilii Ignatiev, Olga Filon, Anna Podolyakina, Victoria Razzhivina, Andrey Andrianov; Moscow City Oncological Hospital No. 1 Named After S.S. Yudin, Moscow, Russian Federation; Clinical Hospital "RZHD-Medicine", St. Petersburg, Russian Federation; SBIH Moscow Clinical Scientific and Practical Center Named After A.S. Loginov of DHM, Moscow, Russian Federation; Moscow City Oncology Hospital 62, Moscow, Russian Federation; Saint Petersburg State University, Saint Petersburg, Russian Federation; I.M. Sechenov First Moscow Medical University, Moscow, Russian Federation; FSBI "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; JSC "Research Lab", Moscow, Russian Federation; State Autonomous Healthcare Institution "Kuzbass Regional Clinical Hospital Named After S.V. Belyaev", Kemerovo, Russian Federation; N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation; Republican Clinical Oncology Dispensary of the Ministry of Health of the Republic of Tatarstan, Kazan, Russian Federation; Clinic No 1 MEDSI, Moscow, Russian Federation; Kaluga Regional Oncology Dispensary, Kaluga, Russian Federation; V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk, Russian Federation; State Budgetary Health Care Institution, Novosibirsk Regional Clinical Oncology Dispensary, Novosibirsk, Russian Federation; JSC R-Pharm, Moscow, Russian Federation

Background: Pembrolizumab is a high-affinity humanized antibody to the PD-1 receptor. This study investigated the efficacy and safety profile of RPH-075, a biosimilar of original pembrolizumab, in patients with advanced skin melanoma. **Methods:** CL01860211 was an international, multicenter, double-blind, randomized, phase III comparative study. The study was based on the following hypothesis: RPH-075 is non-inferior to pembrolizumab (Keytruda) in objective response rate (ORR) at 24 weeks from the start of therapy in patients with unresectable or metastatic melanoma as 1st or 2nd line therapy, not previously treated with pembrolizumab or other anti-PD-1/PD-L1/PD-L2 agents. Pembrolizumab was administered intravenously at a dose of 200 mg Q3W until progression or intolerable toxicity (but no longer than 2 years). ORR was assessed in the per protocol (PP) population according to RECIST 1.1 and iRECIST criteria by an Independent Radiology Review Committee. Disease control rate (DCR), progression-free survival (PFS), were the secondary endpoints. Safety assessment was carried out throughout the study. Adverse events (AE) were assessed by CTCAE v5.0. Immunogenicity was also evaluated over 24 weeks of therapy. **Results:** A total of 266 patients were randomized in 2 groups (n=137 in RPH-075 group and n=129 in pembrolizumab group). The median age was 66 years (range 27–87). The majority of patients had ECOG 0-1 – 96.24%. Most of the patients (90.60%) received pembrolizumab as 1st line treatment. Metastases in the CNS were identified in 10.53% patients. ORR was 28.35% [95% CI: 21.23; 36.73] in RPH-075 group and 24.56% [95% confidential interval (CI): 17.57; 33.21] in pembrolizumab group (p = 0.604). The relative risk was 1.154 [95% CI: 0.755; 1.764]. The lower margin of the obtained 95% CI is higher than the lower margin (0.664) established in the hypothesis. DCR was 48.03% in RPH-075 group and 35.09% in pembrolizumab group (p = 0.057). Median PFS was 3.02 months in RPH-075 group and 2.76 in pembrolizumab group (p = 0.058). Treatment-related adverse events of any grade were registered for 39.13% of patients in RPH-075 group and for 43.75% of patients in pembrolizumab group (p = 0.457). During the main period, anti-drug antibodies (ADA) were detected in 6 patients: 3 (2.36%) in the RPH-075 group and 3 (2.46%) in the pembrolizumab group. None of the patients with detected ADA had neutralizing activity of antibodies to pembrolizumab and no imAEs were registered. **Conclusions:** The non-inferior efficacy of RPH-075 relative to pembrolizumab had been confirmed along with similar safety profile. Clinical trial information: NCT06320353. Research Sponsor: None.

9559 Poster Session

ctDNA versus 18F-FDG PET-CT in predicting long-term disease control in patients with advanced melanoma undergoing immune checkpoint blockade therapy.

Milton Jose De Barros E. Silva, Karina Santiago, Nathalia Carvalho, Rafael Canfield Brianese, Clovis Pinto, Giovana Tardin Torrezan, Fernanda Pintor, Joao Paulo S. N. Lima, Monique Celeste Tavares, Jose Augusto Rinck Jr Jr., Daniel Garcia, João Pedreira Duprat Neto, Dirce Maria Carraro; A.C. Camargo Cancer Center, São Paulo, Brazil

Background: Imaging remains the gold standard for assessing response to systemic immunotherapy in patients with advanced melanoma. Several studies have demonstrated a strong correlation between metabolic response evaluation using 18F-FDG PET-CT and long-term prognosis in patients with advanced melanoma treated with immunotherapy. Meanwhile, ctDNA kinetics has emerged as a promising alternative method to support the evaluation of patients receiving immunotherapy. **Methods:** We prospectively collected blood samples for liquid biopsy assessments using next-generation sequencing (NGS-Ion S5 platform; Thermo Fisher) to detect tumor somatic mutations with a 409-gene panel, and tumor mutations were tracked in plasma samples collected from advanced melanoma patients undergoing immune checkpoint blockade therapy at AC Camargo Cancer Center at baseline, Day 30 (D30), and Day 60 (D60). ctDNA was considered positive if the variant allelic fraction (VAF) exceeded 0.5% and was at least twice that in negative controls. ctDNA results were compared with Day-90 PET-CT and correlated with long-term disease control outcomes. Assessments at D30 and D60 were classified into three categories: molecular responders (MR), molecular non-responders (MNR), and negative pattern (NP), following the framework of the KEYNOTE-942 study. **Results:** This analysis included 15 stage IV melanoma patients treated with nivolumab (3 mg/kg) and ipilimumab (1 mg/kg). Seven patients (47%) showed an objective response on PET-CT. After a median follow-up of 26 months (range: 1–44 months), 31% of patients exhibited controlled disease. PET-CT demonstrated 78% accuracy in predicting long-term disease status (controlled vs. uncontrolled). Baseline ctDNA analysis showed that 10 patients (67%) were ctDNA-positive. The accuracy of baseline ctDNA (positive vs. negative) in predicting long-term disease control status was 71%. On D30, 13 cases were analyzed and classified as follows: 4 (MR), 6 (MNR), and 3 (NP). The accuracy of the D30 liquid biopsy analysis in predicting long-term disease status was only 31%. On D60, 11 cases were analyzed and classified as follows: 5 (MR), 4 (MNR), and 2 (NP). The accuracy of the D60 liquid biopsy analysis in predicting long-term disease status was 73%. **Conclusions:** ctDNA status at baseline and D60, as well as 18F-FDG PET-CT at D90, appear to have similar accuracy in predicting long-term disease control in patients with advanced melanoma treated with immune checkpoint blockade.
Research Sponsor: Oncomine Clinical Research Grant.

9560 Poster Session

Electronic health records (EHR)-based machine learning (ML) approach to predict risk of progression to metastatic melanoma after initial diagnosis.

Ryan Pindale, Katrin Gemmler, Steven Pisano, Ahmad A. Tarhini, Jennifer Rider; ConcertAI, Cambridge, MA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Strategies to predict progression to metastasis in early-stage melanoma patients have relied on a limited sample size and a limited set of clinical or genomic features. Prior studies were able to achieve good discrimination in small cohorts, but applying advanced machine learning techniques to large datasets with deep clinical and molecular data may yield tools with enhanced generalizability and clinical utility. **Methods:** We employed a machine learning approach to predict the likelihood of progression to metastatic melanoma for a cohort with an initial diagnosis of stage 0-3 (n=7477) using both structured and human-curated information in the ConcertAI Patient360 melanoma EHR dataset. Patients with uveal melanoma, a second primary malignancy, or clinical trial participation status were excluded. A total of 68 features including staging, demographic, testing, biomarker, and clinical tumor information recorded within 30 days of initial melanoma diagnosis were used to train several machine learning frameworks to predict the likelihood of progression to metastatic melanoma. A logistic regression, random forest classifier, gradient boosting decision tree, and XgBoost framework were compared using the AUC from a 20% hold-out set to determine the optimal framework after hyperparameter tuning. Additional evaluation metrics, which include accuracy, precision, recall, and F1 were computed for the final model. Feature importance measures were determined using Shapley Additive Explanation (SHAP) dependence plots. Permutation (N=1000) was utilized to evaluate the predictive power of the final model. **Results:** An XgBoost approach produced a test AUC of 0.708 with a pseudo-p value = 0.001 from permutation. Notably, the model produced a precision of 0.709 on the hold-out set. SHAP dependence measures showed that the most important features used for predictions include those involving initial staging and clinical measures of the tumor. Specifically, lower initial stage corresponded with lower predicted probability of metastatic progression. Similarly, higher values of mitotic rate and tumor thickness corresponded with higher predicted probability of progression. In addition, more complex interactions between features also contributed to the improved performance of the XGBoost framework. **Conclusions:** An XgBoost framework trained on a large set clinical features for 7477 melanoma patients predicted metastatic progression with significant predictive power (p = 0.001) yielding an AUC of 0.708. The model relied heavily on staging information at initial diagnosis and information on tumor size, mitotic rate, and ulceration status to make predictions, which were typically reported in unstructured EMR. These results indicate the clinical utility for machine learning models trained on real world data for both providers and patients. Research Sponsor: None.

9561 Poster Session

Delineating the role of the microbiome and tumor microenvironment interactions driving mucosal melanoma (MM) response and resistance to immune checkpoint inhibitor (ICI) treatment.

Florentia Dimitriou, Ashish Damania, Priyadharsini Nagarajan, Sabitha Prabhakaran, Pranoti Sahasrabhojane, Yasmine Hoballah, Devarati Mitra, Roi Weiser, Shirley Y. Su, Ehab Y. Hanna, Bita Esmaeli, Travis T. Sims, Curtis Alvin Pettaway, Rodabe Navroze Amaria, Isabella Claudia Glitza, Nadim J. Ajami, Scott Eric Woodman, Jennifer Ann Wargo, Phillip Andrew Futreal, Jennifer Leigh McQuade; Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Genomic Medicine, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Platform for Innovative Microbiome & Translational Research (PRIME-TR), Moon Shots™ Program, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; Orbital Oncology & Ophthalmic Plastic Surgery, Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Surgery, Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MM is a rare melanoma subtype with distinct biology and low response rates to ICIs. We seek to prospectively profile a cohort of MM patients to determine the interplay of gut, mucosal and tumor microbiome and modifiable risk factors on ICI response and resistance. **Methods:** Patients (pts) with MM presenting at MD Anderson are being prospectively enrolled for longitudinal collection for molecular, microbiome, and lifestyle factor profiling. Planned analyses will evaluate (1) fecal specimens [whole metagenome shotgun (WMS) sequencing, microbiome profiling and 16S rRNA gene sequencing (16S)]; (2) mucosal surface swabs (WMS sequencing); (3) formalin-fixed paraffin embedded (FFPE) tumor specimens [Bruker Digital Spatial Profiling (DSP)]; and (4) fresh tumor samples [whole exome (WES) and whole genome (WGS) of normal and tumor tissue, RNA sequencing, and T cell receptor sequencing]. **Results:** 82 pts with sequenced fecal specimens and mucosal surface swabs were enrolled as of 12/2024. MM primary sites included 25 (30%) naso-oral (including sinonasal), 14 (17%) urogenital, 30 (37%) anorectal, 10 (12%) conjunctival and 3 (4%) other. Disease stages were IVM1a/M1b in 9 (9%) pts, and IVM1c/M1d in 27 (33%) pts. Initial analysis of gut and mucosal surface swabs' microbiome by MM primary site displayed a wide range of intrasample heterogeneity and microbial signatures that correlate with the MM primary site. WES and WGS data analysis indicate low tumor mutational burden (TMB) of 1.34mut/Mb (median, range 0.52 – 14.72). Common mutations included *SF3B1* (23%), *KIT* (15%) and *NRAS* (8%). Anorectal and urogenital tumors contributed to mutational signatures associated with DNA mismatch repair and micro-satellite instability (COSMIC v3.211). Conjunctival and naso-oral tumors showed an association with UV exposure. Results in the gut microbiome analysis from 78 pts treated with ICIs showed compositional differences in the presence and proportion of bacterial taxa in responders (R), compared to non-responders (NR). Distinct bacteria such as *Streptococcus*, *Collinsella*, and *Blautia* were identified in R, and *Butyricicoccus* in NR. DSP analysis by treatment response showed higher expression of CD56 and CD20 in the immune and tumor compartments in R. **Conclusions:** This is an ongoing prospective study that is expected to drive insights into the tumor/microenvironment/host interactions and factors regulating immunogenicity to predict response and resistance to ICIs in a rare and understudied melanoma subtype. Interrogation of the role of the gut microbiome and its modifiable determinants will lead to the investigation of new therapeutic strategies to modulate the microbiome to improve treatment outcomes in MM.
Research Sponsor: U.S. Army Medical Research and Development Command; W81XWH2210973.

9562 Poster Session

Multidimensional, spatially resolved immunologic hallmarks of response to neoadjuvant immune checkpoint blockade (ICB) therapies.

Zichao Liu, Xiaofei Song, Shikhar Dhingra, Wei-Shen Chen, Justin He, Jodi Balasi, Jonathan Nguyen, Carlos Moran-Segura, Joseph Johnson, Chaomei Zhang, Zena Sayegh, Douglas C. Marchion, Sean J. Yoder, Nicholas Reder, Jeffrey H. Chuang, Pei-Ling Chen; The Jackson Laboratory for Genomic Medicine, Farmington, CT; Moffitt Cancer Center, Tampa, FL; Alpenglow Biosciences, Inc., Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX; Vizgen, Cambridge, MA

Background: The groundbreaking neoadjuvant ICB clinical trials have established beyond doubt that ICB before surgery will become the new standard of care for metastatic melanoma. Importantly, the shift from radiographic to pathologic response scoring offers an unprecedented window of opportunity to interrogate a goldmine of 'on-treatment' biospecimens. To date, single-cell profiling and region-based spatial transcriptomics (ST) have highlighted the importance of tertiary lymphoid structures (TLS) and stem-like T-cells as positive predictors of ICB response. However, the molecular mechanisms by which tumor infiltrating lymphocytes communicate and organize multicellular immune hubs within the spatial context of the tumor ecosystem remains poorly understood. **Methods:** To identify robust biomarkers of response to neoadjuvant ICB, we assembled a cohort of 58 stage III melanoma patients treated with neoadjuvant ICB [24 ipilimumab-nivolumab (IPI-NIVO), 21 NIVO-relatlimab (RELA), 13 PD1 mono] and deployed transformative technologies and computational methods, including single-cell FFPE sequencing, multiplexed FISH single-cell ST (MERFISH 305 genes), digital pathology, 3D open-top light-sheet imaging and AI-based computational pathology, to decipher the complex neoadjuvant ICB tumor ecosystem in response to therapy. We also developed 2 critical computational tools, SCIRA (Spatial Cellular Interaction and Receptor Activation), to compute receptor-ligand (R-L) interactions in whole slide images, and GC-SCAN (graph-based spatial clustering against noise), a graph-based algorithm that quantifies locally clustered structures from spatial -omics data. **Results:** Our results showed that the quantity and size of hyper-expanded germinal center/TLS, with increased GC: non-GC B-cell ratio, plasma cells and spatially resolved stem-like T-cells are strongly associated with response. IPI-NIVO elicited significantly stronger GC proliferation compared to NIVO-RELA and PD1 monotherapy, suggesting anti-CTLA4 can robustly induce germinal center/TLS proliferation. SCIRA spatial R-L analyses revealed the critical chemokine R-L interactions that organize the GC- and T-cell zones in response to therapy. Lastly, 3D light-sheet imaging revealed remarkable morphologic heterogeneity in 3D, with interconnected GC-TLS networks that are indicative of long-range molecular gradients. **Conclusions:** Our investigations herein have provided a comprehensive characterization of the immune architectures, cellular communications and 3D large-scale morphologic organizations of the TME that drive response to neoadjuvant ICB therapy. We believe the results of this study will enable the development of robust predictive biomarkers to guide the design of next generation combination ICB therapies in the clinical trial setting for melanoma and other cancer types. Research Sponsor: None.

Long-term outcomes following melanoma metastasectomy categorized by response to immune checkpoint inhibitor (ICI) therapy.

Aravind Sreeram, Sabrina Lin, Katherine Panageas, Parisa Momtaz, Monica F. Chen, Edmund Bartlett, Mary Susan Brady, Michael A. Postow, James William Smithy, Charlotte Eielson Ariyan, Alexander Noor Shoushtari, Danielle M. Bello; Johns Hopkins University School of Medicine, Baltimore, MD; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

Background: Patients undergoing surgical resection of Stage III/IV melanoma after response to ICIs show favorable survival, particularly with pathologic complete response (pCR). However, long-term outcomes of such patients stratified by ICI response remain undescribed. As surgery is increasingly employed in both PD-1 sensitive and refractory settings (e.g. tumor-infiltrating lymphocytes (TIL) therapy), better-defined outcomes and a clearer understanding of surgery's role are much needed. **Methods:** Patients treated with ICI (2003-2023) followed by metastasectomy were identified from a prospectively maintained database. Pre-surgery ICI response was assessed radiographically, and patients were categorized as having either stable/responding disease (R), an isolated site of disease progression (IP), or multiple progressing sites of disease (MP) for which surgery was pursued due to acute symptoms or palliative intent. Clinicopathologic factors examined included response to ICI, resection to no evidence of disease (NED), and pCR. Kaplan-Meier analyses with log-rank tests were used to compare disease-specific survival (DSS) from surgery date. Cox proportional hazards models identified independent predictors of DSS. **Results:** Among 513 patients, 426 (83%) had stage IV and 87 (17%) had stage III disease at ICI initiation. Patients were categorized as either R (n=76), IP (n=227), or MP (n=210). Fifty-three percent of patients received subsequent systemic therapy including 20 TIL patients, 12 of whom were in the MP group. Median follow-up after surgery among survivors was 2.51 years (IQR 0.93, 6.72). Median DSS following surgery was 4.1 years (95% CI: 2.5, NR). Resection to NED at the first operation post-ICI (n = 202, 39%) was associated with improved 5-year DSS [81% (75%, 88%) vs. 26% (20%, 33%); $p < 0.001$], with similar findings in only Stage IV patients (n = 426) [75% (67%, 84%) vs. 24% (19%, 32%); $p<0.001$]. Patients who underwent resection for an R or IP tumor had a 5-yr DSS of 89% (80%, 98%) or 62% (55%, 70%), respectively, compared to 20% (14%, 28%) for MP lesions ($p < 0.001$). Independent predictors of DSS also included NED resection and pCR (Table 1). **Conclusions:** Disease control after metastasectomy following ICI is durable, especially in patients with responding, stable, or isolated progressing disease, in addition to those achieving resection to NED or pCR. Alternative therapeutic strategies should be considered for patients with MP tumors as DSS remains poor after surgery alone. Research Sponsor: None.

Multivariate model of DSS.

	p-value	HR [95% CI]
NED Status	**<0.001**	0.31 [0.20, 0.49]
Pre-operative Neutrophil-Lymphocyte Ratio	**0.014**	1.02 [1.01, 1.04]
Response to ICI (R, IP, MP)	**<0.001**	1.31 [0.65, 2.65] (R v. IP) 2.75 [1.35, 5.63] (R v. MP)
pCR Status	**<0.001**	0.22 [0.08, 0.65]
Surgery Site	0.074	1.33 [0.97,1.83]
Time from ICI Initiation to Surgery	**0.006**	0.85 [0.76, 0.97]
M Stage	**0.003**	2.01 [1.21, 3.34]

Immunological phenotype as a predictor for response after isolated limb perfusion for patients with melanoma in-transit metastasis.

Anna Constantinescu, Roger Olofsson Bagge, Anne Huibers; Sahlgrenska Centre for Cancer Research, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; Gothenburg University, Gothenburg, Sweden

Background: Isolated limb perfusion (ILP) is a regional treatment for patients with melanoma in-transit metastases (ITM) confined to extremities, using a high dose of melphalan. ILP has a high response rate, with approximately 60% having a complete response (CR). This study aimed to validate if pre-operative immunological phenotype could be a predictive factor for CR after ILP. **Methods:** A total of 132 patients undergoing ILP as a first treatment for melanoma ITM between January 2012 and March 2023 were included in this study. The number and percentage of naïve and memory T and B cell subtypes, as well as natural killer (NK) cells were characterized by analyzing pre-operative blood samples using fluorescence activated cell sorting (FACS). Univariable and multivariable analysis were used to investigate if any of these subtypes were predictive for response after ILP. **Results:** Out of the 132 patients included in the study, 53% achieved a CR. Immunological and clinical factors significantly and independently associated with an CR after ILP were: number of metastases (OR 0.98, 95% CI 0.97-1.00, p=0.036), size of largest metastases (OR 0.96, 95% CI 0.93-0.99, p=0.009), percentage of CD3+8+ cells (OR 1.07, CI 95% 1.02-1.13, p=0.012) and percentage of CD3+8+45RA+ cells (OR 1.11, CI 95% 1.01-1.22, p=0.029). **Conclusions:** Immunological phenotype described as percentage of cytotoxic T-cells and naïve cytotoxic T-cells are together with tumor burden important predictive factors for response after ILP for patients with melanoma in-transit metastasis. This could potentially contribute to better patient selection and individualized treatment algorithms, but might also be a foundation for future novel treatment combinations, where an ongoing trial is currently combining ILP with a PD-1 inhibitor (ClinicalTrials.gov NCT03685890). Research Sponsor: None.

Anxiety, depression, fear of cancer recurrence (FCR) and health-related quality of life (HRQL) in people with melanoma receiving adjuvant therapies.

Julia Elizabeth Lai-Kwon, Michael Jefford, Ashkan Mehrnejad, Mustafa Abdi Mohamed, Kortnye Maureen Smith, Lavinia Anne Spain, Aparna Dodla Rao, Belinda Lee, George Au-Yeung, Allison Drosdowsky, Karla Gough, Shahneen Sandhu; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Department of Medical Oncology, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia; Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Department of Medical Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia

Background: One year ofadjuvant anti-programmed cell death protein-1 (anti-PD1) or dabrafenib-trametinib are standards of care for patients (pts) with resected stage III-IV melanoma. Emotional distress has been linked to inferior disease outcomes following neo-adjuvant immunotherapy for stage III melanoma. We aimed to assess the anxiety, depression, FCR and HRQL in a real-world population up to 2 years post initiation of adjuvant therapy. **Methods:** A prospective, longitudinal study of pts with resected stage IIB-IV melanoma receiving adjuvant anti-PD1 or dabrafenib-trametinib at an Australian comprehensive cancer center. The Patient-Reported Outcomes Measurement Information System (PROMIS) Network Emotional Distress-Anxiety 7a and Depression 8b, Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF), and Functional Assessment of Cancer Therapy-General (FACT-G) were collected pre-treatment, and at 1, 3, 6, 12, and 24 months post treatment initiation. PROMIS t-scores were categorized as mild (55-59), moderate (60-69) and severe (≥70). Clinically significant FCR was categorized as a FCRI-SF score ≥22. **Results:** From September 2021-December 2024, 70 pts were eligible and 52 (74%) consented: 17 (33%) female, median age 64 years (IQR 60-71), 46 (89%) resected stage III, 32 (62%) on adjuvant anti-PD1. 41 pts had completed treatment and 11 were still receiving treatment at data cut off (17 December 2024). 51 pts completed at least 1 set of surveys. The prevalence of mild, moderate or severe anxiety, depression and clinically significant FCR up to 2 years post initiation of adjuvant therapy is shown in the table. People experiencing anxiety or depression at 24 months reported worse HRQL compared to those without (mean FACT-G score- anxiety: 67.8 vs 82.8; depression: 69.7 vs 84.2). Of the 18 pts with data at both 12 and 24 months, all those with clinically significant FCR at 12 months continued to report FCR at 24 months. All those with clinically significant FCR at 24 months reported worse HRQL compared to those without clinically significant FCR at 24 months (mean FACT-G score: 67.7 vs 80.5). **Conclusions:** A significant number of pts report anxiety, depression, and clinically significant FCR up to 2 years post initiation of adjuvant therapy, which is associated with worse HRQL. Screening for psychological issues can identify those who may benefit from psychological and/or pharmacological intervention to improve disease outcomes. Research Sponsor: None.

	Pre-treatment (n= 51)	1 month (n= 46)	3 months (n=44)	6 months (n= 38)	12 months (n=31)	24 months (n=18)
Anxiety (n, %)	20 (40%)	19 (41%)	16 (36%)	15 (39%)	13 (42%)	7 (39%)
Depression (n, %)	16 (31%)	17 (37%)	13 (30%)	17 (45%)	14 (45%)	9 (50%)
Clinically significant FCR (n, %)	10 (20%)	12 (26%)	9 (20%)	10 (26%)	6 (19%)	5 (28%)

9567 Poster Session

Identification of patients at high risk for relapse by Merlin assay (CP-GEP) in an independent cohort of melanoma patients (pts) that did not undergo sentinel lymph node biopsy: An H&N subgroup analysis.

Teresa Amaral, Eftychia Chatziioannou, Alica Nuebling, Tobias Sinnberg, Heike Niessner, Ulrike M. Leiter, Djvalini Dwarkasing, Tim Arentsen, Christian Groß, Alexander M. Eggermont, Lukas Flatz, Stephan Forchhammer; Skin Cancer Center, Eberhard Karls University of Tübingen, Tübingen, Germany; Center for Dermatooncology, Department of Dermatology, Eberhard Karls University of Tübingen, Tübingen, Germany; Center for Dermatooncology, Eberhard Karls University of Tübingen, Tübingen, Germany; Skin Cancer Center, Department of Dermatology, Eberhard Karls University of Tuebingen, Tuebingen, Germany; Department of Dermatology, Center for Dermatooncology, Eberhard Karls University of Tübingen, Tübingen, Germany; SkylineDx, Rotterdam, Netherlands; SkylineDx BV, Rotterdam, Netherlands; University Medical Center Utrecht & Princess Máxima Center, Utrecht, Netherlands; Department of Dermatology, Eberhard Karls University of Tuebingen, Tuebingen, Germany

Background: Sentinel lymph node biopsy (SLNB) is still the gold standard for nodal assessment used in the clinical staging of cutaneous melanoma (CM) pts by AJCC v8. Recently, we showed in a small cohort that CP-GEP also has the potential to risk stratify pts who did not undergo SLNB in low and high-risk for recurrence (Amaral et al, EJC 2023). SLNB may be challenging in pts with head and neck (H&N) melanoma, due to the regional course of cranial nerves and lymphatic drainage. Here we focus on the ability of CP-GEP to stratify pts with H&N melanoma in particular those with lentigo maligna, who did not undergo SLNB, for their risk of recurrence. **Methods:** We analyzed formalin-fixed paraffin-embedded primary tumor samples of 930 pts of which 206 were localized in the H&N region, with stage I/II CM diagnosed between 2000-2017 who did not receive SLNB. The CP-GEP model used combines the expression of 8 genes (SERPINE2, GDF15, ITGB3, CXCL8, LOXL4, TGFBR1, PLAT and MLANA) by quantitative reverse transcription polymerase chain reaction with age and Breslow thickness to obtain a binary output: CP-GEP Low- or High-Risk. Relapse-free survival (RFS), distant metastasis free survival (DMFS) and Melanoma Specific Survival (MSS) were evaluated using Kaplan-Meier curves. **Results:** We included 930 pts (stage IA-IIC) of which 206 pts (22.3%) were diagnosed with H&N melanoma. Patient characteristics: 41% were females, median age was 73-year-old, median Breslow thickness was 0.5 mm and 75.6% were lentigo maligna melanomas. Median follow up was 51 months (RFS). All H&N pts showed the following survival: 5-year RFS 82.5%, DMFS 94.0 and MSS 95.5%. CP-GEP risk stratification identified 17 patients as CP-GEP High-Risk and 188 as CP-GEP Low-Risk. The 5-year RFS rate was 86.7% for CP-GEP Low-Risk and 39.7%% for CP-GEP High-Risk pts (HR 7.85; $p<0.001$), 5-year DMFS was 96.3% for CP-GEP Low-Risk and 68.9% High-Risk pts (HR 10.26; $p<0.001$) and the 5-year MSS was 98.5% for CP-GEP Low-Risk pts and 64.7% for CP-GEP High-Risk pts (HR 24.45; $p<0.01$). **Conclusions:** Pts with H&N CP-GEP Low-Risk tumors have a good long-term survival compared to High-Risk pts even though SLN status was not assessed. This prognostic information may allow the clinicians to skip SLNB in this difficult anatomic localization and in frail and/or older pts. Research Sponsor: SkylineDx.

Distinct effect of neoadjuvant PD1 alone, PD1+IPI, and PD1+lenvatinib in the peripheral immune profile of melanoma patients (pts) and correlation with pathological (path) response.

Ines Esteves Domingues Pires da Silva, Jordan W. Conway, Akshaya Ramanathan, Laura Smith, Nurudeen A. Adegoke, Jorja Braden, Maria Gonzalez, Richard A. Scolyer, Umaimainthan Palendira, Matteo S. Carlino, Christian U. Blank, Alexander M. Menzies, Georgina V. Long; Melanoma Institute Australia, The University of Sydney, Sydney, Australia, Wollstonecraft, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Sydney, NSW, Australia; The University of Sydney, Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, NSW, Australia; The University of Sydney, Sydney, NSW, Australia; Sydney Medical School, Faculty of Medicine and Health Sciences, The University of Sydney, Camperdown and Melanoma Institute Australia, Sydney, and Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Westmead, NSW, Australia; The Netherlands Cancer Institute, Amsterdam, Netherlands; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia

Background: Neoadjuvant immunotherapy (NeoIT) has significantly improved clinical outcomes for pts with macroscopic stage III resectable melanoma and is the current standard of care for these pts. Here, we analysed longitudinal peripheral immune profiles and their correlation with path response for 3 different PD1-based NeoIT regimens. **Methods:** Pts with macroscopic stage III resectable melanoma treated with neoadjuvant PD1-based regimens (PD1 alone, PD1+IPI and PD1+Lenvatinib) for 6 weeks, followed by surgery, were included. Cytometry by time-of-flight (CYTOF; 39-marker panel) was performed on peripheral blood mononuclear cells (PBMCs) at baseline and week 6 (wk 6; pre-surgery). **Results:** Of 64 pts included, 17 PD1 alone (7 [41%] had major pathological response [MPR; $\leq$ 10% of viable tumour cells at the surgical specimen]), 26 PD1+IPI (20 [77%] had MPR) and 21 PD1+Lenvatinib (12 [57%] had MPR). We analysed >200 peripheral immune cell types/phenotypes, and present the statistically significant treatment effects (from baseline to wk 6), overall and based on path response (MPR vs. non-MPR), in patients treated with PD1 alone, PD1+IPI and PD1+lenvatinib (see Table). **Conclusions:** IPI+PD1 and PD1+Lenvatinib induced stronger peripheral blood immune activation, compared with PD1 alone, irrespective of path response. There were differences in the MPR vs non-MPR pts, particularly for PD1 alone. A more in-depth analysis of the effects of these PD1-based regimens and their association with recurrence is underway to identify key immune cell types/phenotypes associated with response & resistance to NeoIT. Research Sponsor: None.

Effect of neoadjuvant PD1 alone, PD1+IPI and PD1+lenvatinib in the peripheral immune profile of melanoma patients.

	Overall treatment effect	MPR (vs. non-MPR)	Non-MPR (vs. MPR)
PD1	Increase in: - OX40+ / ICOS+ regulatory T cells (Tregs) - KI67+ ICOS+ CD4 T cells	Increase in: - GZM+ CD4+ & CD8+ T cells - Double negative [CD27- IgD-] B cells	Increase in: - Non-classic [CD14low+CD16++] HLA-DR+ monocytes Decrease in: - CD4 T effector memory cells - Th1 cells
PD1+IPI	Increase in: - Tregs - Activated [ICOS+ / LAG3+ / TIGIT+] CD4+ T cells - TIM3+ CD4+ & CD8+ T cells - Non-classic [CD14low+CD16++] monocytes - Cytotoxic [CD56dim CD16+] NK cells Decrease in: - Stem-like [TCF7+] CD4+ & CD8+ T cells		Increase in: - OX40+ / T-BET+ CD127- CD8+ T effector memory cells
PD1+lenvatinib	Similar changes seen with PD1+IPI, as well as an increase in: - Th1 - Th17 - CD8+ T effector memory cells Decrease in: - Double negative [CD27- IgD-] B cells	Increase in: - CD127- Tregs	Increase in: - HLA-DR+ non-classic [CD14low+CD16++] monocytes

9569 Poster Session

Rational use of adjuvant anti-PD-1: Multi-omics model of recurrence in stage III melanoma.

Tuba Nur Gide, Nurudeen A. Adegoke, Michael Xie, Yizhe Mao, Grace Heloise Attrill, Nigel Maher, Robyn P.M. Saw, Ismael A. Vergara, Matteo S. Carlino, Serigne N. Lo, Ines Esteves Domingues Pires da Silva, Jorja Braden, Alexander M. Menzies, Richard A. Scolyer, Georgina V. Long, James S. Wilmott; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, and Royal Prince Alfred Hospital, and The Mater Hospital Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, Australia; Melanoma Institute Australia, Faculty of Medicine and Health Sciences, The University of Sydney, and Westmead and Blacktown Hospitals, Westmead, Sydney, NSW, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, and Royal Prince Alfred Hospital, Sydney, NSW, Australia

Background: Stage III melanoma patients (pts) undergoing adjuvant anti-PD-1 immunotherapy have a high risk of recurrence (43% within one year) and treatment-related adverse events (25% severe). This study developed multi-omics models that accurately identify pts at high risk of recurrence who may benefit from alternative treatment strategies or closer surveillance. **Methods:** We analyzed a cohort of 131 pts with stage III melanoma (47% IIIA/B and 53% IIIC/D) who received adjuvant anti-PD-1 therapy. The nodal burden was micrometastatic (35%) and macrometastatic (54%), with in-transit metastases in 11% of pts. Comprehensive multi-omics profiling included DNA sequencing (tumor mutational burden [TMB]), whole-transcriptome sequencing (gene expression profiling [GEP]), and multiplex immunohistochemistry (tumor microenvironment [TME]) of the baseline tumor sample. We developed predictive models for 12-month recurrence using multivariable penalized logistic regression with consensus-nested cross-validation incorporating clinical, TMB, GEP, and TME features. Internal validation was performed using optimism bias through 500 bootstrap iterations. **Results:** Clinical factors (nodal burden, stage, and site of primary melanoma) alone achieved a modest AUC of 0.66 (95% CI: 0.56-0.75) for predicting recurrence. Addition of TME features, particularly CD16+ cells interacting with PD-L1+CD16+ macrophages, significantly improved predictive accuracy (AUC: 0.81, 95% CI: 0.72-0.91). Further enhancements were observed with TMB and BRAF mutation status (AUC: 0.83, 95% CI: 0.74-0.92) and GEP-derived natural killer (NK) cell and interferon-gamma (IFNg) signatures (AUC: 0.83, 95% CI: 0.73-0.93). A consensus model integrating these features achieved an optimal AUC of 0.86 (95% CI: 0.78-0.94). This model demonstrated robust performance across macroscopic (AUC: 0.88, 95% CI: 0.78-0.98) and microscopic (AUC: 0.86, 95% CI: 0.70-1.00) nodal diseases. **Conclusions:** This study demonstrates the potential of multi-omics profiling to significantly enhance recurrence risk prediction in stage III melanoma pts receiving adjuvant anti-PD-1 therapy. We developed a robust model with high predictive accuracy by integrating clinical data with TME, TMB, and GEP features (AUC, 0.86). This model can help identify pts at high risk of recurrence who may benefit from alternative treatment strategies or closer surveillance. Research Sponsor: None.

AUC scores of various models.

Model	AUC
Clinical	0.66
Clinical+TME	0.81
Clinical+TMB	0.83
Clinical+GEP	0.83
Consensus Model	0.86

Combining machine learning with the immunohistochemical expression of AMBRA1 and loricrin to identify non-ulcerated AJCC stage I/II melanomas at high-risk of metastasis.

Penny Lovat, Sydney Grant, Tom William Andrew, Gyorgy Paragh, Philip Sloan, Marie Labus, Jane Armstrong; Newcastle University, Newcastle upon Tyne, United Kingdom; AMLo Biosciences, Newcastle upon Tyne, United Kingdom; Roswell Park Comprehensive Cancer Centre, Buffalo, NY; Royal Victoria Infirmary, Newcastle Upon Tyne, Newcastle upon Tyne, United Kingdom; University of Sunderland, Sunderland, United Kingdom

Background: Precision-based personalised biomarkers able to identify both low-risk and high-risk patient subpopulations with localised cutaneous melanoma are urgently needed to guide clinical follow up and treatment stratification. The combined immunohistochemical expression of AMBRA1 and Loricrin (AMBLor) in the epidermis overlying non-ulcerated AJCC stage I/II melanomas as prognostic biomarker able to accurately identify genuinely low-risk patient subpopulations (NPV >96%, clinical sensitivity >95%, Ewen *et al* Brit J Dermatol. 2024). To further identify distinct subsets of patients at high risk of metastasis, the present study aimed to develop a machine learning (ML) risk-prediction model combining AMBLor 'at-risk' status with six specific patient clinical and tumour pathological features. **Methods:** Using common and widely used ML models a Naïve Bayes and a Generalized Linear Model with adaBoost, ML algorithms were trained and tested using three geographically distinct retrospective-prospective cohorts of AMBLor at-risk non-ulcerated AJCC stage I/II melanomas from Australia, USA and Spain (n=552), with validation studies performed in a 4^{th} independent retrospective-prospective cohort of 120 AMBLor at-risk non-ulcerated localised melanomas derived from the UK. **Results:** Based on a training: test data split of 50:50, 20% of patients were defined as high-risk, with a 5-year recurrence-free survival (RFS) probability of 56% (Log-rank [Mantel-Cox) $P < 0.0001$, HR 6.88, 95% CI 3.03-15.63, clinical specificity 87.2%, PPV 44.4%). Further validation of the ML algorithms in the UK validation cohort identified 24% patients as high-risk, with a 5-year RFS of 56.3% (Log-rank [Mantel-Cox) $P < 0.0001$, HR 7.59, 95% CI 2.94-19.6, clinical specificity 82.1%, PPV 50%). **Conclusions:** Through the proven negative predictive power of AMBLor with the cumulative power of prognostic clinical and pathological features these data provide a novel and improved risk- prediction model to stratify patients with non-ulcerated localised melanomas at low or high risk of tumour recurrence thereby aiding optimal personalised patient management and treatment stratification. Research Sponsor: Newcastle University; AMLo Biosciences.

9571 Poster Session

Longitudinal ctDNA monitoring for post-surgical molecular residual disease in patients with stage I-IIIb melanoma.

George Ansstas, Karam Khaddour, Sumedha Sudhaman, Karen Lin, Griffin Budde, Andrew Stewart Poklepovic, Bently Patrick Doonan, Meghan Mooradian, Ryan J. Sullivan, Vincent The-Luc Ma, Jeremy Rosiecki, Steven Y. Liu, Ronald L. Drengler, Daniel Blake Flora, Georgia Beasley, Kristen Elizabeth Rhodin, John Robert Hyngstrom, Elise Kornreich Brunsgaard, Minetta C. Liu, Alan Tan; Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Natera, Inc., Austin, TX; Massey Cancer Center, Virginia Commonwealth University, Richmond, VA; University of Florida College of Medicine, Gainesville, FL; Division of Medical Oncology, Massachusetts General Hospital, Boston, MA; Division of Hematology, Medical Oncology, and Palliative Care, Department of Medicine, University of Wisconsin, Madison, WI; Alaska Oncology And Hematology, LLC, Anchorage, AK; Start Center for Cancer Care, San Antonio, TX; St Elizabeth Medical Center, Edgewood, KY; Department of Surgery, Duke Cancer Center, Duke University, Durham, NC; Department of Surgery, Duke Cancer Center, Duke University,, Durham, NC; Division of Surgical Oncology, Rush University Medical Center, Chicago, IL; Rush University Medical Center, Chicago, IL

Background: Circulating tumor DNA (ctDNA) has emerged as an important biomarker for early recurrence detection and monitoring disease status in patients with cancer, including melanoma. Here, we evaluate the prognostic value and utility of post-operative ctDNA detection in patients with stage I-IIIb melanoma using a clinically validated, personalized, tumor-informed ctDNA assay. **Methods:** We conducted a retrospective analysis of real-world data of patients with stage I-IIIb melanoma (N=197), including ctDNA results using a personalized, tumor-informed, 16-plex mPCR-NGS assay (Signatera, Natera, Inc.). Adjuvant treatment decision and post-surgical plasma (N=1,718) sample collection during treatment for ctDNA analysis was at the provider's discretion. ctDNA results were correlated with clinical outcomes. **Results:** Across 197 patients analyzed for ctDNA, a median of 7 tests (range: 2-44) per patient were performed over a median period of 24.7 months (range: 3.7-74.7).ctDNA-positivity at any postoperative timepoint was significantly associated with shorter relapse-free survival (RFS; hazard ratio [HR]: 15.0, 95% CI: 7.3–31.0, $P < 0.0001$). This finding was pronounced for patients with distant/regional recurrence (HR: 27.0, 95% CI: 10.0–71.0, $P < 0.0001$). Multivariate analysis confirmed ctDNA-positivity to be the most significant prognostic factor associated with RFS when compared with other clinicopathologic factors such as adjuvant treatment, stage, sex, and mitotic rate (N=163, HR: 10.50, 95% CI: 3.891–28.32 $P < 0.001$). Finally, we explored the utility of ctDNA-positivity and its impact on clinical decision-making and observed that ctDNA-positivity influenced changes in treatment management in 73.7% (N=28/38) of patients, ranging from imaging escalation to treatment initiation, switch, or escalation. **Conclusions:** Our findings highlight the prognostic value of post-surgical, personalized ctDNA detection and monitoring of molecular residual disease in stage I-IIIb melanoma and provide information on real-world clinical decision practices based on ctDNA changes. Research Sponsor: None.

Efficacy of adjuvant anti-PD-1 antibodies and interferon in patients with nail apparatus melanoma: A retrospective, multicenter study (ADJ-NAIL study).

Takaya Komori, Eiji Nakano, Yukiko Kiniwa, Shoichiro Mori, Sotaro Yamamoto, Hiroshi Kato, Shusuke Yoshikawa, Koji Yoshino, Megumi Aoki, Tatsuya Takenouchi, Takuya Maeda, Keijun Yoshino, Shuichi Ohe, Kenta Nakama, Hideyuki Ishikawa, Yoshiyuki Nakamura, Toshihiro Takai, Takamichi Ito, Yasuhiro Nakamura, Shigeto Matsushita; Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Saitama, Japan; Department of Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan; Shinshu University, Matsumoto-Shi, Japan; Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan; Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan; Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; Sizuoka Cancer Center, Shizuoka-Shi, Japan; Department of Dermatologic Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Dermato-Oncology, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan; Department of Dermatology, Niigata Cancer Center Hospital, Niigata, Japan; Department of Dermatology, Faculty of Medicine, Graduate School of Medicine, Hokkaido University, Sapporo, Japan; Department of Dermatology, Chiba University Graduate School of Medicine, Chiba, Japan; Department of Dermatologic Oncology, Osaka International Cancer Institute, Osaka, Japan; Department of Dermatology, Kurume University School of Medicine, Kurume, Japan; Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; Department of Dermatology, Hyogo Cancer Center, Akashi, Hyogo, Japan; Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka, Japan

Background: The clinical efficacy of anti-PD-1 antibodies (PD-1) for nail apparatus melanoma (NAM) is less effective than that for advanced cutaneous melanoma. Despite the significant need for effective adjuvant (adj) therapies to improve survival in NAM, the efficacy of adj PD-1 and interferon (IFN) is unknown because of the rarity of NAM. Thus, this study aimed to investigate the efficacy of adj PD-1 and adj IFN therapies for NAM. **Methods:** Thisretrospective study reviewed data of patients with stage IIB, IIC, and III NAM without adj therapies (observation: OBS), who received adj PD-1 therapy (adj-PD-1) and adj IFN therapy (adj-IFN) after complete resection across 42 Japanese institutions. The Kaplan–Meier analysis and multivariable Cox proportional hazard models were used to estimate survival probabilities. Propensity-score matching (PSM) was employed to adjust for differences in the baseline characteristics between each group. **Results:** A total of 397 patients with NAM (OBS, n = 219; adj-PD-1, n = 99; adj-IFN, n = 79) were included. The baseline characteristics were significantly different among the three groups in terms of age ($P < 0.001$) and stage ($P < 0.001$). The other baseline characteristics were comparable. A significant difference was noted in the recurrence-free survival (RFS) among the OBS, adj-PD-1, and adj-IFN groups (5-year RFS 42% vs. 21% vs. 48%; $P = 0.02$). However, distant metastasis-free survival (DMFS) and overall survival (OS) were not significantly different among the three groups (5-year DMFS 50% vs. 44% vs. 54%; $P = 0.15$, 5-year OS 59% vs. 46% vs. 58%; $P = 0.28$). Multivariable Cox proportional hazard models revealed that adj-PD-1 and adj-IFN did not positively affect survival outcomes compared with OBS (adj-PD-1: RFS hazard ratio [HR] 1.14; $P = 0.47$, DMFS HR 1.04; $P = 0.84$, OS HR 1.19; $P = 0.50$, adj-IFN: RFS HR 0.73; $P = 0.11$, DMFS HR 0.77; $P = 0.21$, OS HR 0.96; $P = 0.84$). After PSM, the patient backgrounds were balanced at a 1:1 ratio between the OBS and adj-PD-1 groups (n = 71 each) and adj-IFN groups (n = 75 each). No significant differences were found in the survival outcomes between the OBS and adj-PD-1 groups (5-year RFS 30% vs. 20%; $P = 0.96$, 5-year DMFS 39% vs. 39%; $P = 0.95$, 5-year OS 49% vs. 39%; $P = 0.53$) and between the OBS and adj-IFN groups (5-year RFS 35% vs. 48%; $P = 0.06$, 5-year DMFS 41% vs. 54%; $P = 0.09$, 5-year OS 56% vs. 57%; $P = 0.73$). In patients who experienced a relapse and were treated with nivolumab/ipilimumab combination therapy, the progression-free survival from the initiation of combination was significantly shorter in the adj-PD-1 group than in the OBS group (median PFS 1.8 months vs. 4.0 months; $P = 0.03$). **Conclusions:** In NAM, adj-PD-1 and adj-IFN did not improve survival. Furthermore, the use of adj-PD-1 may attenuate the efficacy of nivolumab/ipilimumab combination therapy after relapse. Research Sponsor: National Cancer Center Research and Development Fund; 2023-J-03; Japan Agency for Medical Research and Development; JP24ck0106765h0003.

9573 Poster Session

The 31-gene expression profile as a guide to better risk-aligned care decisions for patients with stage I–III cutaneous melanoma: An NCI-SEER analysis.

Merve Hasanov, Brian Martin, Sonia K. Morgan-Linnell, Christine N. Bailey, Valentina I. Petkov, David Hyams; The Ohio State University Comprehensive Cancer Center, The James, Columbus, OH; Castle Biosciences, Inc., Friendswood, TX; National Cancer Institute, Rockville, MD; Desert Surgical Oncology, Rancho Mirage, CA

Background: Current management guidelines for cutaneous melanoma (CM) are based on AJCC staging to stratify patients into risk groups. However, this approach can result in under- and over-estimation of risk for individual patients. The 31-gene expression profile (31-GEP) test has been prospectively validated to provide a more personalized likelihood of sentinel lymph node positivity, as well as risk of recurrence, distant metastasis, and mortality, than AJCC staging alone (Class 1A=low risk, Class 1B/2A=intermediate risk, and Class 2B=high risk). Using expanded SEER registry cohorts, we assessed the ability of the 31-GEP to independently stratify patients with high and low mortality risk categories, and to evaluate whether 31-GEP testing itself was associated with improved patient outcome. **Methods:** SEER registry data for patients with stage I–III CM (2013–2019) were linked to patients with 31-GEP test results provided by Castle Biosciences (N=13,560) using a registry trusted independent third party. Five-year melanoma-specific survival (MSS) was estimated using Kaplan-Meier analysis; survival differences between groups were compared using log-rank test. Multivariable analysis was performed to determine significant predictors of melanoma-specific mortality (MSM). Survival differences between 31-GEP tested and untested patients were performed by matching tested and untested patients according to clinicopathological factors, diagnosis year, ethnicity, and socioeconomic status. **Results:** Patients with a Class 1A 31-GEP result had a significantly higher 5-year MSS than those with Class 1B/2A or Class 2B results (99.1%, 92.5%, vs. 85.9%, $p<0.001$). Multivariable analysis showed that a Class 2B result (HR=4.20, $p<0.001$), Class 1B/2A result (HR=3.21, $p<0.001$), a positive lymph node (HR=2.78, $p<0.001$), Breslow thickness (HR=1.10, $p=0.001$), ulceration (HR=1.41, $p=0.033$), age (HR=1.04, $p<0.001$), and mitotic rate (HR=1.05, $p=0.022$) were significant predictors of MSM. In staging subset analyses, patients with a Class 1A 31-GEP result had a significantly higher 5-year MSS than those with Class 2B results in stage I-IIA CM (1A=98.8%, 1B/2A=95.5% vs. 2B=93.0%, $p<0.001$), stage IIB–IIC CM (1A=94.2%, 1B/2A=91.2% vs. 2B=82.3%, $p=0.002$), and stage III CM (1A=94.8%, 1B/2A=75.0% vs. 2B=77.6%, $p<0.001$). Among all stages, 31-GEP-tested patients had a lower MSM (HR=0.68, $p<0.001$) than untested propensity score-matched patients. **Conclusions:** In a large, real-world cohort of clinically tested patients with stage I–III CM, the 31-GEP stratified mortality risk within all staging groups, which could better help clinicians and patients make risk-aligned treatment and clinical management decisions. Research Sponsor: Castle Biosciences, Inc.

Comparison of surveillance circulating tumor DNA and Merkel polyomavirus antibody titer for detection of Merkel cell carcinoma recurrence.

Joshua Elbridge Chan, Daniel S. Hippe, Manisha Thakuria, Tomoko Akaike, Song Youn Park, Ann W. Silk, Karam Khaddour, Paul Nghiem, Lisa C. Zaba; Stanford University School of Medicine, Stanford, CA; Fred Hutchinson Cancer Research Center, Seattle, WA; Brigham and Women's Hospital, Boston, MA; University of Washington, Seattle, WA; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Stanford University Medical Center and Cancer Institute, Department of Dermatology/Cutaneous Oncology, Palo Alto, CA

Background: Circulating tumor DNA (ctDNA) is emerging as a robust biomarker for detecting recurrences in Merkel cell carcinoma (MCC). This study aims to compare the performance of ctDNA against the Merkel polyomavirus antibody titer (AMERK) test in predicting MCC recurrence risk. **Methods:** We conducted a longitudinal, multi-center observational study involving 171 MCC patients undergoing disease surveillance, including serial ctDNA and AMERK testing (median testing interval: 92 days). All patients had detectable antibodies by AMERK at initial diagnosis and both tests were conducted within 45 days of each other. ctDNA tests were classified as positive if ctDNA was $>$ 0 MTM/mL. An AMERK test was positive if antibody titers rose $\geq$ 30% from the prior titer. Clinical recurrences were identified through routine imaging and clinical examinations. The diagnostic performance of ctDNA and AMERK tests was assessed using positive and negative predictive values (PPV and NPV), recurrence-free survival after any positive test vs. all negative tests, and corresponding hazard ratios (HRs) from Cox regression. **Results:** 718 pairs of ctDNA and AMERK tests were collected from 171 patients. Over a median follow-up of 445 days, there were 38 clinical recurrences, 91/718 (13%) positive ctDNA tests, and 73/718 (10%) positive AMERK tests. A significantly increased clinical recurrence rate was observed in patients with a positive ctDNA test compared to those with consistently negative results (HR: 27.4, 95%CI: 11.0-68.3) (Table 1). Although a positive AMERK test was similarly associated with higher clinical recurrence (HR: 5.8, 95%CI: 3.0-11.1), the rate was distinctly lower than that for a positive ctDNA test (HR: 5.8 vs. 27.4; $p < 0.001$). The PPV for clinical recurrence at 1 year after a positive test was significantly higher for ctDNA vs. AMERK (PPV: 73% [95% CI: 58-84%] vs. 51% [95% CI: 29-70%]; p=0.014). NPV for recurrence within 4 months of a negative test for the ctDNA test was similarly higher for ctDNA vs. AMERK (NPV: 98% [95% CI: 97-99%] vs. 95% [95% CI: 92-97%]; p=0.001). The median lead time between the first positive test and a clinically detected recurrence was 3.1 months for ctDNA (among 30 recurrences preceded by a positive test) and 1.9 months for AMERK (among 19 recurrences preceded by a positive test) (p=0.063). **Conclusions:** Our results indicate that, in a cohort of AMERK positive patients, ctDNA outperforms AMERK for detection of MCC recurrence. ctDNA may be a viable alternative to AMERK in clinical practice and may better identify high-risk patients who benefit from more aggressive monitoring or adjuvant therapy trials. Research Sponsor: None.

Hazard ratios for subsequent MCC clinical recurrence: Comparison of positive ctDNA and AMERK tests.

Test	HR	(95% CI)	P-value
Positive ctDNA	27.4	(11.0, 68.3)	<0.001
Positive AMERK	5.8	(3.0, 11.1)	<0.001
Difference (ctDNA / AMERK)	4.7	(2.1, 15.9)	<0.001

9575 Poster Session

Overall survival outcomes in stage III melanoma patients treated with adjuvant immunotherapy vs targeted therapy: A National Cancer Database analysis.

Siavash Bolourani, Mark B. Faries, Omid Hamid, Justin Tyler Moyers; Providence Saint John's Cancer Institute, Santa Monica, CA; The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA

Background: Adjuvant therapy with immunotherapy (IO) and targeted therapy (TT) has significantly improved outcomes in Stage III melanoma following surgical resection. While both approaches demonstrate efficacy, head-to-head comparisons remain limited, and real-world evidence on overall survival (OS) across diverse subgroups is sparse. This study compares OS between adjuvant IO and TT using data from the National Cancer Database (NCDB) from 2018 to 2020, offering insights into subgroup-specific benefits. **Methods:** We conducted a retrospective cohort study of Stage III melanoma patients from the NCDB diagnosed between 2018 and 2019 who underwent definitive surgical resection followed by either IO or TT. Patients receiving neoadjuvant therapy were excluded. OS was analyzed using Kaplan-Meier survival curves and compared using log-rank tests. Hazard ratios (HR) with 95% confidence intervals (CI) were derived from Cox proportional hazards models, adjusted for demographic and clinical covariates. Subgroup analysis was performed to identify populations deriving differential benefit from IO. **Results:** A total of 1,493 patients met the inclusion criteria (IO: 1,352; TT: 141). Overall survival (OS) was significantly higher in the IO group (74.9%; 95% CI: 72.2–77.8% at 3 years) compared to the TT group (62.1%; 95% CI: 52.5–73.3% at 3 years) ($p = 0.0055$). Subgroup analysis revealed that the survival benefit with IO was more pronounced in patients aged <65 years (HR 0.49; 95% CI: 0.32–0.75), males (HR 0.54; 95% CI: 0.37–0.77), those with private insurance (HR 0.45; 95% CI: 0.27–0.76), and primary tumors located on the head and neck (HR 0.44; 95% CI: 0.22–0.89). No subgroup demonstrated superior outcomes with TT. **Conclusions:** In this NCDB-based analysis, adjuvant IO was associated with a significant OS advantage compared to TT in Stage III melanoma patients. However, NCDB limitations, including lack of information on specific agents (e.g., BRAF/MEK inhibitors or checkpoint inhibitors), must be acknowledged. Additionally, this analysis reflects OS rather than melanoma-specific survival (MSS). In the NCDB sample, there was a 10:1 preference for IO over TT, reflecting marked community preference for IO. These findings appear to indicate that IO is the preferred adjuvant strategy, though further prospective studies are required to validate subgroup-specific outcomes and confirm these results. Research Sponsor: None.

Survival impact of adjuvant treatment in resected stage III cutaneous melanoma patients: Results from a real-life cohort study (TAMARIS).

Charlee Nardin, Théo Erard, Mona Amini Adle, Henri Montaudie, Julie Charles, Marc Puyraveau, Geraldine Jeudy, Philippe Bernard, Florent Grange, Delphine Legoupil, Ouidad Zehou, Philippe Célérier, Candice Lesage, Francois Aubin, Amir Khammari, Gaelle Quereux, RIC-Mel; Université de Franche-Comté, Inserm 1098 RIGHT, Besançon, France; University Hospital Jean Minjoz, Besancon, France; Centre Léon Bérard, Lyon, France; Dermatology Department, Université Côte d'Azur, CHU de Nice, Nice, France; Dermatology Departement, CHU Grenoble Alpes, France, University Grenoble Alpes INSERM U 1209, CNRS UMR 5309, Institut for Advanced Biosciences Grenoble, Grenoble, France; Centre de Méthodologie Clinique, CHU, Besançon, France; Department of Dermatology, Dijon University Hospital, Dijon, France; CHU Dupuytren, Limoges, France; Centre Hospitalier Universitaire de Reims–Hôpital Robert Debre, Reims, France; CHRU Brest - Hôpital Morvan, Brest, France; APHP Henri Mondor, Dermatology, Créteil, France; Dermatology Department, La Rochelle-Ré-Aunis Hospital Group, La Rochelle, France; Dermatology Departement, CHU de Montpellier, Montpellier, France; Dermatology Department, CHU de Besançon, Besançon, France; Oncodermatology Department, Nantes University Hospital, Nantes, France; Nantes University Hospital, Skin Cancer Unit, Nantes, France

Background: Anti-PD-1 immunotherapies and BRAF+MEK inhibitors (BRAFi/MEKi) (specifically for BRAF V600E/K-mutant melanoma) have been shown to improve recurrence-free survival (RFS) in patients (pts) with resected stage III metastatic melanoma in phase III trials. However, none of these studies has demonstrated a significant improvement in overall survival (OS). Notably, adjuvant BRAFi/MEKi therapy has shown better OS only in the BRAF V600E subgroup of patients. In this context, we evaluated the real-world impact of adjuvant therapies on OS. **Methods:** TAMARIS is a national multicenter retrospective study designed to evaluate the efficacy of adjuvant treatment (anti-PD-1 or BRAFi/MEKi) in pts with resected AJCC 8th edition stage III melanoma using data from the French RIC-Mel prospective database. The primary endpoint was OS analyzed using the Kaplan-Meier method, comparing pts who received adjuvant treatment (adjuvant group) within 3 months of surgery to those who did not (control group). Demographic and clinical characteristics were compared using chi-square analyses. Secondary endpoints included OS in specific subgroups and RFS. **Results:** A total of 1,172 pts (median age: 65 years [IQR: 53–74]) with resected stage III melanoma were included between 2018 and 2023. Among them, 796 pts (68%) received adjuvant treatment with anti-PD-1 (n=676) or BRAFi/MEKi (n=120). The median treatment duration was 10.8 months (IQR: 5.6–11.9). Most pts had a history of SSM (54%) with a median Breslow thickness of 2.8 mm [range, 0-47] and stage IIIB (31%) or IIIC disease (49%). Surgical interventions for metastases prior to adjuvant treatment included lymph node dissection in 53% of cases, sentinel lymph node biopsy in 38%, and cutaneous metastasis resection in 8%. Pts in the control group were older (median age: 69.7 vs. 63.0 years, $p < 0.0001$). The median follow-up was 30.4 months (IQR: 16.7-43.3). OS was significantly longer in the adjuvant group compared to the control group (HR: 0.617; 95% CI: 0.474-0.802; p = 0.0003), with a 2-year OS of 90% (95% CI: 88-92) in the adjuvant group versus 79% (95% CI: 74-83) in the control group. There was a trend toward better OS with BRAFi/MEKi compared to anti-PD-1 (HR: 0.569; 95% CI: 0.312-1.037; p = 0.065). Subgroup analyses demonstrated a significant positive impact of adjuvant treatment on OS across most subgroups, except for pts aged ≤75 years, those with stage IIIA disease, primary melanomas with a Breslow thickness <2.8 mm, or without ulceration. RFS also favored the adjuvant group (HR: 0.545; 95% CI: 0.458-0.649; $p < 0.0001$), with a 2-year RFS of 67% (95% CI: 63-70) and 45% (95% CI: 40-50) in the control group. **Conclusions:** Adjuvant treatment appears to provide an OS benefit in patients with resected stage III melanoma in real-world settings. Further research is required as age-related differences may influence prognosis. Research Sponsor: None.

Financial toxicity and employment outcomes in people with melanoma receiving adjuvant therapies.

Julia Elizabeth Lai-Kwon, Michael Jefford, Ashkan Mehrnejad, Mustafa Abdi Mohamed, Kortnye Maureen Smith, Lavinia Anne Spain, Aparna Dodla Rao, Belinda Lee, George Au-Yeung, Allison Drosdowsky, Karla Gough, Shahneen Sandhu, ASCO Authors 2025; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Peter MacCallum Cancer Centre, Melbourne, Australia

Background: One year ofadjuvant anti-programmed cell death protein-1 (anti-PD1) or dabrafenib-trametinib are standards of care for patients (pts) with resected stage III-IV melanoma. The impact of adjuvant therapy on a pt's employment, income, and level of financial toxicity are unknown. We examined these outcomes up to 2 years post initiation of adjuvant therapy. **Methods:** A prospective, longitudinal study of pts with resected stage IIB-IV melanoma receiving adjuvant anti-PD1 or dabrafenib-trametinib at an Australian comprehensive cancer center. Two customized employment surveys assessed impact on employment and income. Survey 1 (7 items) was administered pre-treatment, Survey 2 (11 items) at 12 and 24 months post treatment initiation. The Comprehensive Score for Financial Toxicity (FACIT-COST) was collected pre-treatment and at 1, 3, 6, 12, and 24 months post treatment initiation. FACIT-COST scores were categorized into none (≥26), mild (14-25), moderate (1-13) and severe (0) financial toxicity. **Results:** Between September 2021-December 2024, 70 pts were eligible and 52 (74%) consented: 17 (33%) female, median age 64 years (IQR 60-71), 46 (89%) had resected stage III, 32 (62%) on adjuvant anti-PD1. 41 pts had completed treatment and 11 were still receiving treatment at data cut off (17 December 2024). Employment surveys were completed by 51 pts pre-treatment, 31 at 12 months and 18 at 24 months. Most (18/31, 58%) were working at 12 months, with the majority (17/18, 94%) in the same job as pre-treatment. Only half (9, 50%) were working the same number of hours or earning the same income (10, 56%) as pre-treatment (the remainder, less). Barriers to returning to work at 12 months were ongoing symptoms (45%), financial concerns (26%), and work environment (21%). 18 pts completed both the 12 and 24 month surveys. 9 (50%) had returned to work by 12 months and the majority (n=8) were still working at 24 months. At 24 months, 6 (75%) were working the same number of hours but only 5 (63%) were earning the same income as pre-treatment (the remainder, less). The prevalence of financial toxicity is shown in the table and ranged from 16% at 6 months to 36% at 12 months. **Conclusions:** Half of pts reported reduced working hours and income 12 months post therapy initiation, mostly due to ongoing symptoms. A third reported financial toxicity at 12 months, even with universal healthcare. This data can inform shared decision-making about risks and benefits of adjuvant therapy and highlights the importance of screening for financial toxicity to identify pts who require support. Research Sponsor: None.

FACIT-COST category	Pre-treatment (n= 51)	1 month (n=46)	3 months (n=44)	6 months (n=38)	12 months (n=31)	24 months (n=18)
None	37 (72.5)	32 (69.6)	35 (79.5)	32 (84.2)	20 (64.5)	13 (72.2)
Mild	13 (25.5)	11 (23.9)	6 (13.6)	5 (13.2)	10 (32.3)	2 (11.1)
Moderate	1 (2.0)	2 (4.3)	3 (6.8)	1 (2.6)	1 (3.2)	3 (16.7)
Severe	0	1 (2.2)	0	0	0	0
Any	14 (27.5)	14 (30.4)	9 (20.5)	6 (15.8)	11 (35.5)	5 (27.8)

A pooled analysis of clinical outcomes with anti-PD1-based neoadjuvant immunotherapy (NeoIT) in cutaneous squamous cell carcinoma (cSCC).

Ines Esteves Domingues Pires da Silva, Vincent The-Luc Ma, Susmita Reddy Karri, Michael Lowe, Ronen Stoff, Andrea Boutros, Nessr Abu Rached, Samrin Liaqat, Teresa Amaral, Charlee Nardin, Janice M. Mehnert, Caroline Gaudy-Marqueste, Eva Muñoz Couselo, Christian B. Agbisit, Ignasi Martim, Lucie Heinzerling, Matthew Stephen Block, Matteo S. Carlino, Serigne N. Lo, Karam Khaddour; Melanoma Institute Australia, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia; Division of Hematology, Medical Oncology, and Palliative Care, Department of Medicine, University of Wisconsin, Madison, WI; Westmead and Blacktown Hospital, Sydney, NSW, Australia; Emory University School of Medicine, Atlanta, GA; Mayo Clinic, Rochester, MN; University of Genoa, Genova, Italy; Ruhr University Bochum, Bochum, NA, Germany; Fiona Stanley Hospital, Perth, Western Australia, Australia; Skin Cancer Center, Eberhard Karls University of Tübingen, Tübingen, Germany; University Hospital Jean Minjoz, Université de Franche-Comté, Inserm RIGHT, Besançon, France; Perlmutter Cancer Center of NYU Langone Health/NYU Grossman School of Medicine, New York, NY; Aix-Marseille University, CHU Timone, Marseille, France; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; Hospital Clinic de Barcelona, Barcelona, Spain; Department of Dermatology, Ludwig-Maximilians-Universität München, München, Germany; Department of Oncology, Mayo Clinic, Rochester, MN; Sydney Medical School, Faculty of Medicine and Health Sciences, The University of Sydney, Camperdown and Melanoma Institute Australia, Sydney, and Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Westmead, NSW, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; Dana-Farber Cancer Institute, Boston, MA

Background: Anti-PD1 immunotherapy has shown improved clinical outcomes in patients (pts) with advanced cSCC, and recently, in the neoadjuvant setting for resectable disease. Pathological (path) response is predictive of recurrence in melanoma and recent NeoIT trials suggests the same in cSCC; however, an analysis of clinical outcomes in pts with resectable cSCC treated with intended anti-PD1-based NeoIT in larger datasets remains unknown. **Methods:** Pts with resectable cSCC treated with intended anti-PD1-based NeoIT from 17 cancer centres globally were included. Baseline patient and disease characteristics, treatment regimen, path response and recurrence-free survival (RFS) or progression-free survival (PFS) were collected and examined. **Results:** 134 pts with resectable cSCC were treated with intended anti-PD1-based NeoIT. Median age was 75 years old (range, 39-97), 72% (n=97) were male. One fifth (22%, n=29) were immunocompromised and 43% (n=58) had ECOG PS of ≥1. Of 125 (93%) pts with known primary cSCC, 82% (n=102) were from the head & neck. Most pts (79%, n=106) were stage III/IV. The majority had anti-PD1 monotherapy (91%, n=122) and 9% (n=12) had anti-PD1+/-investigational agent. Median follow-up from commencement of NeoIT was 10 months (95% CI, 9 - 12). Nearly half of the pts (49%, n=66) underwent surgery; 37 (56%) pts had major pathological response (MPR; ≤10% viable tumour cells at the surgical specimen; 31 [47%] had complete path response [0% of viable tumour cells] and 6 [9%] had near complete path response [1-10% of viable tumour cells]), 6 (9%) had partial path response (pPR; >10% and ≤50% of viable tumour cells), and 23 (35%) had path non-response (pNR; >50% of viable tumour cells). Of the 66 pts who underwent surgery, 11% (n=7) had recurrence (5 loco-regional and 2 distant recurrence), all non-MPR pts (1 pPR and 6 pNR). 12-months RFS was improved with MPR vs non-MPR (100% vs 79%, p=0.004). 52% (n=34) pts had adjuvant treatment (23 anti-PD1 alone, 7 anti-PD1+/-investigational agent, 2 platinum and 2 cetuximab). Within non-MPR pts, 12 had adjuvant treatment (3 recurred; 25%), while 17 did not have adjuvant treatment (4 recurred; 24%). Fifty-one percent (n=68) of pts did not have surgery; 9 (13%) due to progressive disease (PD) and 53 (78%) due to clinical response. Of the 53 pts with a clinical response, 5 (9%) subsequently progressed. Fourteen (10%) pts have died, 6 (4%) related to cSCC; 2 had surgery (non-MPR) and 4 did not have surgery (all due to PD). **Conclusions:** Anti-PD1-based NeoIT is an active regimen in resectable stage II-IV cSCC and is associated with high clinical response and MPR rates. No pts with MPR from NeoIT has recurred to date, however, 9% of pts who did not have surgery due to clinical response eventually progressed. These findings highlight the importance of further research to investigate the role of surgery in this subgroup of patients. Research Sponsor: None.

9579 Poster Session

Use of artificial intelligence to identify high risk profiles in early stage melanoma patients from pathology slides.

Christina Kanaan, Céline Bossard, Severine Roy, Naima Benannoune, Naima Hamoudi, Ines Besraoui, Magali Lacroix-Triki, Jérôme Chetritt, Caroline Robert; Department of Pathology, Gustave Roussy, Villejuif, France; Pathology Department, IHP Group, Nantes, France; Gustave Roussy, Villejuif, France; Gustave Roussy, Department of Medical Biology and Pathology, IHU-National PRecISion Medicine Center in Oncology, Villejuif, France

Background: To refine prognostication in primary cutaneous melanoma (CM) and optimize adjuvant treatment decisions, we evaluate SmartProg-MEL (SPM), an AI-based histology-driven algorithm developed by DiaDeep and applied to H&E-stained whole-slide images (WSI) at the time of diagnosis. SPM provides a risk stratification score, under 15 minutes, for overall survival (OS) and relapse-free (RFS) outcomes to support clinical decision-making. **Methods:** SPM was evaluated on a retrospective cohort of 383 primary CM with 5-year follow-up (46% IA, 15% IB, 9% IIA, 7% IIB, 6% IIC, 13% III, 4% IV). The model stratifies patients into high- or low-risk groups based solely on the WSI of the primary tumor. Kaplan-Meier curves are used to compare RFS and OS between risk groups, with statistical significance assessed using the log-rank test. A multivariable Cox regression analysis was performed to evaluate the independent prognostic value of SPM after adjusting for pathological factors. The negative and positive predictive values (NPV and PPV) of the SMP are explored. **Results:** Patients with a low risk score had a significantly higher 5-y OS and RFS than patients of the high risk group (93.1% vs 62.5%, $p<0.001$ and 92.8% vs 47.1%, $p<0.001$). In multivariable analysis, SPM risk score was the strongest predictor (OS: HR=3.95, $p<0.005$, RFS: HR=5.03, $p<0.005$). In the I-IIA group, 29% (n=78) were assigned to the high risk profile with a decrease of the OS and RFS compared with the low risk group (OS: 95.4% vs 86%, $p<0.05$; RFS: 94.3% vs 74%, $p<0.01$). SPM has a NPV of 96%, 100% and a PPV of 17% and 69% in stages I/IIA and IIB/C respectively. **Conclusions:** The AI-based risk stratification algorithm, SPM, demonstrates greater performance than stage in identifying high and low risk profiles, especially in early-stage CM patients. This new prognostic tool opens avenues for a routine clinical application to precise therapeutic decisions in an adjuvant setting. Research Sponsor: None.

Cohort statistics: Event occurrences and five-year OS and RFS endpoints survival rates, segmented by AJCC stage and SPM risk stratification.

		RFS		OS	
	# patients	# events (%)	5-y RFS [CI]	# events	5-y OS [CI]
I/IIA	266	21	88.1 [82.1 to 92.2]	14	92.5 [87.6 to 95.6]
SPM Low Risk	188 (70.7%)	8(38.1%)	94.3 [88.9 to 97.2]	5(35.7%)	95.4 [89.8 to 98.1]
SPM High Risk	78(29.3%)	13(61.9%)	74.1 [58.4 to 84.4]	9 (64.3%)	86.1[73.8 to 92.8]
IIB/IIC	51	34	24.3 [11.7 to 39.3]	22	47.8 [31.2 to 62.7]
SPM Low Risk	1 (2.0%)	0(0.0%)	100 N/D	0 (0.0%)	100 N/D
SPM High Risk	50(98.0%)	34(100.0%)	22 [9.7 to 37.4]	22 (100.0%)	46.6 [29.9 to 61.7]
III	49	39	32.8 [19.3 to 47.2]	25	100 N/D
SPM Low Risk	5(10.2%)	2(5.1%)	60.1 [12.6 to 88.2]	2(8.0%)	60.1 [12.6 to 88.2]
SPM High Risk	44(89.8%)	34(87.2%)	29.5 [14.4 to 42.3]	20 (80.0%)	51.4 [35.2 to 65.4]

SPM: DiaDeep SmartProg-MEL; CI: confidence intervals.

9580 Poster Session

Identification of novel RNA biomarkers for the differential diagnosis of cutaneous melanoma and nevi.

Igor Samoylenko, Andrew R. Zaretsky, Oleg V. Drozd, Lidia V. Chudakova, Oksana E. Garanina, Irena L. Shlivko, Sergey A. Yargunin, Grigorii Zinovev, Kirill A. Baryshnikov, Igor Sinelnikov, Irina N. Mikhaylova, Yana Vishnevskaya, Kristina V. Orlova, Lev V. Demidov; FSBI "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; Department of Molecular Technologies Research Institute of Translational Medicine N. I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; Department of Molecular Technologies Research Institute of Translational Medicine N. I. Pirogov Russian National Research Medical University of the Ministry of, Moscow, Russian Federation; Federal State Budgetary Educational Institution of Higher Education Privolzhsky Research Medical University of the Ministry of Health of the Russian Federation, Nizhny Novgorod, Russian Federation; State Budgetary Healthcare Organisation "Clinical Oncology Dispensary No.1" under the Ministry of Healthcare of Krasnodar region (SBHI COD No. 1), Krasnodar, Russian Federation; Petrov National Research Institute of Oncology, Saint Petersburg, Russian Federation; Melanoma Unit Russia "Israeli Medical Research Center", Moscow, Russian Federation; N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

Background: The differential diagnosis of nevi and melanomas remains a significant clinical challenge, as misclassification can result in overtreatment or delayed care. Despite advances in clinical, dermatoscopic, and histopathological methods, benign lesions are frequently misclassified as nevi, SAMPUS, or MELTUMP, while atypical melanomas are often mistaken for nevi. This study aimed to identify novel RNA markers for the differential diagnosis of nevi and melanomas. **Methods:** Ninety histological samples of melanocytic neoplasms were analyzed, including 45 morphologically confirmed nevi and 45 melanomas. Massive parallel sequencing was performed using the NextSeq 550 system (Illumina, USA) with the "NextSeq High Output 150 Cycles Kit" reagent set, following the manufacturer's protocol. Data normalization employed FPKM and TPM metrics, and differential gene expression analysis utilized 26 algorithms on the RNA-Seq 2G web server. Selected RNA markers were further validated on an independent cohort of 120 samples (60 verified nevi and 60 melanomas) using RT-PCR. **Results:** The study analyzed the expression of over 18,000 coding and 42,000 non-coding RNAs (primarily long non-coding) in histologically confirmed melanomas and nevi, balanced between "classical" and dysplastic nevi. Initial RNA-Seq quality control confirmed high data integrity and sufficient sequencing depth in 87 of 90 samples. Melanoma-specific markers identified included CSAG1, CXCL1, CXCL8, CXCL9, DUXAP8 + DUXAP9 + DUXAP10, FCRL3, IGHA1, IGHG1, LRP2, MAGEA3 + MAGEA6 + MAGEA12, MMP1, OR2I1P, SPP1, and VGF, while nevus-specific markers included CD44-AS1, CDR1-AS (LINC00632), DSCAS, and ENSG00000287270. For RNA marker testing at the next stage, all 120 samples were deemed suitable for analysis. Modeling of multimarker tests achieved an AUROC of 0.94, with a model incorporating only 5 preselected markers outperforming those with a larger number of markers. The most informative logistic regression model included the following marker combinations: MAGEA3 + MAGEA6, CXCL8 + LINC00632, DUXAP8 + DUXAP9 + DUXAP10, CSAG1, and CXCL1. **Conclusions:** The model, incorporating only 5 markers, achieved an AUROC of 0.94 in an independent validation cohort. It is now positioned for further validation in cohorts enriched with samples of uncertain malignant potential based on histological evaluation. Clinical trial information: NCT04353050. Research Sponsor: Ministry of Health of the Russian Federation.

9581 Poster Session

Animated patient's guide to melanoma: Assessing patient understanding, shared decision-making, and health outcomes.

Kyleigh LiPira, Michael B. Atkins, Rekha T. Chaudhary, Laura Ferris, Sapna Pradyuman Patel, Miriam Kadosh, Stephanie Searle; Melanoma Research Foundation, Washington, DC; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; University of Cincinnati, Cincinnati, OH; The University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Colorado Comprehensive Cancer Center, Aurora, CO; Mechanisms in Medicine, Toronto, ON, Canada

Background: Patients with melanoma who participate in informed, personalized-care discussions with their healthcare providers are better prepared to carry out shared decision-making (SDM) and achieve best attainable health outcomes. In a 2018 Cancer Registry Experience study of 114 melanoma survivors, a majority of respondents did not feel knowledgeable or prepared to discuss treatment options with their healthcare team. The complexity of melanoma treatments and patients' limitations due to poor health literacy are obstacles to SDM. In November 2018, the *Melanoma Research Foundation* introduced *An Animated Patient's Guide to Melanoma (APGM)*, an online resource aimed at improving patient knowledge, informed SDM, and achieving best outcomes. **Methods:** APGM was developed with highly visual formats of learning on a website, comprised of melanoma educational animations, expert videos, patient experience videos, slide shows, infographics, and self-assessment tools. Learners on the website have the option to voluntarily participate in evaluations, including pop quizzes and surveys. From the website, learner responses were collected from surveys over a period of 72 months, ending January 2025. Patient responses to these questions were aggregated to measure outcome-based questions, and patient intention to discuss key decisions with healthcare providers. **Results:** Our 6-year reported data is based on 443,015 total views and 272,191 unique visitors aggregated from the APGM online resource. Unique US visitors were 54% (N=146,983); and 46% (N=125,208) from other countries. In terms of US participants/learners: 72% (N=105,828) were patients; 12% (N=17,638) were family and caregivers; 6% (N=8,819) were healthcare providers; and 10% (N=14,698) were other/undisclosed. Of the respondents who volunteered to complete the surveys, 95% (N=1,059) were patients who reported they '*will use information learned to better self-manage their melanoma*'; 93% (N=969) of patients '*will discuss information learned with their doctor*'; and 95% (N=694) of patients '*will discuss melanoma treatment options with their doctor*'. **Conclusions:** Our data shows that animated formats of learning tailored to the needs and learning styles of patients with melanoma provide effective translational learning resources, improve self-management skills, and facilitate engagement in SDM. Visual formats of learning are effective resources in helping inform patients with melanoma and improving outcomes. Our APGM initiative validates the utility of visual formats of learning which may be utilized in other oncology settings to benefit patient outcomes. Research Sponsor: None.

A phase II trial of perioperative oral itraconazole for the management of low risk basal cell carcinoma.

Rodrigo Perez Pereira, Dienifer Hermann Sirena, Sergio Jobim Azevedo, Tiago Elias Heinen, Renato Marchiori Bakos, Mariani Magnus Andrade, Monique Maria Franco da Silva, Charles Francisco Ferreira; Unidade de Pesquisa Clínica em Oncologia, Porto Alegre, Brazil; Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Background: Recently, new treatment options have emerged for advanced basal cell carcinoma (BCC), including oral Hedgehog pathway inhibitors like Vismodegib. Itraconazole has also shown promising clinical activity in these cases by targeting the SMO receptor. This study aimed to assess the clinical and molecular efficacy of oral Itraconazole in BCC patients with low-risk disease. **Methods:** Patients with localized BCC who were eligible for surgical excision were enrolled. They received 200 mg of Itraconazole twice daily for 60 days prior to resection. Clinical assessments were based on the RECIST 1.1 criteria, with target lesions measuring at least 10 mm following a confirmatory biopsy. Molecular markers associated with cellular activity and angiogenesis (Ki67, GLI, CD105) were evaluated using immunohistochemical staining. Adverse effects were graded according to NCI-CTC v4. **Results:** A total of 26 patients were treated, with 61% female and a mean age of 62 years. The most common BCC subtype was nodular (54%), and the most frequent tumor location was the trunk (65%). Patients presented with stable disease (92%), partial response (4%), and complete response (4%). Notably, no disease progression occurred during the treatment period, and all patients underwent the planned surgical excision. The median tumor diameter prior to treatment was 14 mm (range: 11–16 mm), and after treatment, it was 13 mm (range: 11–15 mm). This reduction was statistically significant, as determined by the Wilcoxon test ($p < 0.0001$). Additionally, biological activity of Itraconazole was demonstrated through the measurement of Ki67, GLI, and CD105. The percentage of the stained area for CD105 or Endoglin decreased significantly following Itraconazole treatment, from 0.11 [0.01–1.86] to 0.03 [0.00–0.22], with this reduction also being statistically significant ($p \leq 0.0001$). **Conclusions:** Preoperative oral Itraconazole demonstrated both clinical and molecular activity in localized, low-risk BCC lesions, with no patients showing disease progression and two patients exhibiting partial and complete responses, respectively. The median tumor diameter significantly decreased after the treatment period. In addition to the reduction in tumor size, there was a notable decrease in the expression of CD105, marking the first study to demonstrate this correlation in this context. Endoglin, a well-established marker for endothelial cell proliferation, particularly in angiogenesis in regenerating tissues or inflamed tumors, underscores the antiangiogenic potential of Itraconazole. These findings align with previously published results and suggest that oral Itraconazole could be a promising candidate for managing low-risk BCC, while also opening the opportunity for further investigation in advanced disease settings. Clinical trial information: NCT03972748. Research Sponsor: None.

Comparison of the tolerability and safety of hedgehog inhibitors in real-life: A cohort of 330 patients with locally advanced basal cell carcinoma.

Florian Herms, Mourad Djermane, Marie Beylot-Barry, Cendrine Chaffaut, Sophie Dalac, Olivier Dereure, Jean-Jacques Grob, Celeste Lebbe, Laurent Mortier, Jerome Lambert, Nicole Basset-Seguin; APHP, Hôpital Saint Louis, Paris, France; Hôpital Saint Louis, Paris, France; Hopital Saint-André, Bordeaux, France; CHU de Dijon, Dijon, France; University of Montpellier, Montpellier, France; Aix-Marseille University, Hôpital de la Timone, Marseille, France; Université de Paris, AP-HP Hôpital Saint-Louis, Paris, France; CHU Lille, Lille, France; ECSTRA, Centre de Recherche en Epidémiologie et Statistiques, INSERM UMR 1153, Paris, France

Background: Two hedgehog pathway inhibitors (HHIs) have been approved for the treatment of locally advanced basal cell carcinoma (laBCC): vismodegib and sonidegib. Efficacy of both seem similar, even though no head-to-head comparison has been performed. However, adverse events (AEs) in pivotal trials seemed less frequent with a later onset with sonidegib. CARADERM is a French national database created in 2013 to improve the management of rare skin tumors, including laBCC. The objective of our study was to compare the safety profile of HHIs in this real-life cohort. **Methods:** LaBCC patients from the CARADERM database were reviewed. Patients who started either vismodegib or sonidegib at least one year before analysis were included. Type and grade of AEs were collected when available. Cumulative incidence of the first occurrence of adverse events was estimated, with treatment discontinuation as a competing event. **Results:** In the total cohort of 452 laBCC patients, 330 met the inclusion criteria: 280 (85%) treated with vismodegib and 50 (15%) with sonidegib. The median follow-up was 22.3 months. Clinical characteristics (including age, gender, performance status, localization and tumor size) were similar for both groups. The cumulative incidence of the first AE was significantly lower with sonidegib (43.5%, 95% confidence interval (95%CI) = 29.0-57.2 at 12 months) than with vismodegib (63.5%, 95%CI = 57.5-68.9 at 12 months, p=0.0014) (Table 1). For vismodegib treated patients, 191 (68%) experienced at least one AE. The most frequent were cramps (n=123, 44%), dysgeusia (n=123, 44%) and alopecia (n=88, 31%). For sonidegib treated patients, 22 (44%) experienced at least one AE. The most frequent were cramps (n=8, 16%), alopecia (n=7, 14%) and dysgeusia (n=6, 12%). Major AEs seemed to be less frequent and to appear later with sonidegib, with a significant difference for cramps (p=0.007) and dysgeusia (p=0.001), but not significant for alopecia (p=0.059). **Conclusions:** We present here the largest real-life comparison of HHIs in a real-life cohort of laBCC patients. The cumulative incidence of the first AE was significantly lower with sonidegib. Even though the range of AEs was similar with both HHIs, dysgeusia and cramps were less frequent with sonidegib. These data highlight the difference in terms of tolerance of both HHIs, with a later onset and lower frequencies of AEs with sonidegib. However, though both groups were clinically comparable, vismodegib was overrepresented compared to current prescriptions of HHIs, and further analyses are mandatory to confirm these data. Research Sponsor: None.

Cumulative incidence of first adverse event at 3, 6 and 12 months.

	3 months [95CI]	6 months [95CI]	12 months [95CI]
Sonidegib	16.3 % [7.5 ; 28.0]	26.8 % [15.2 ; 39.8]	43.5 % [29.0 ; 57.2]
Vismodegib	31.6 % [26.2 ; 37.2]	55.5 % [49.5 ; 61.2]	63.5 % [57.5 ; 68.9]

95CI = 95% confidence interval.

9584 Poster Session

Sensitivity of circulating tumor DNA (ctDNA) for disease recurrence or relapse in melanoma patients.

Vincent The-Luc Ma, Fauzia Hollnagel, Madison S. Harris, Janmesh D. Patel, Matthew C. Mannino, Jennifer L. Schehr, Alexander Birbrair, Joshua Michael Lang, Shuang Zhao; Division of Hematology, Medical Oncology, and Palliative Care, Department of Medicine, University of Wisconsin, Madison, WI; University of Wisconsin Madison, Madison, WI; University of Wisconsin, Madison, WI; University of Wisconsin School of Medicine & Public Health, Madison, WI; University of Wisconsin Carbone Cancer Center, Madison, WI

Background: ctDNA has emerged as a biomarker for minimal residual disease (MRD) detection in colorectal cancer and other cancer types. Its role in MRD monitoring and disease detection for melanoma patients merits further investigation. We aimed to assess the sensitivity of a commercially available ctDNA test to detect recurrence or relapse in patients with melanoma. **Methods:** A retrospective cohort analysis was performed using a personalized, tumor-informed, ctDNA assay (Natera) on prospectively collected plasma from patients with a diagnosis of melanoma from December 2021 to January 2025 with longitudinal follow up. Inclusion criteria were patients with no evidence of disease (NED) following definitive surgery or clinical remission with systemic therapy; and an undetectable ctDNA level. We evaluated the sensitivity of ctDNA detection of patients who had biopsy and/or radiographic confirmation of recurrence or relapse; and further stratified this based on anatomic sites of recurrence or metastasis (mets). Sensitivity was computed and logistic regression models were conducted to assess predictors of ctDNA detection. **Results:** 116 patients met the inclusion criteria. 48% (n=56) had confirmed recurrence or relapse. Among these patients, 82% (n=46) had NED following surgery and 18% (n=10) had clinical remission with systemic therapy. 75% (n=42) were resected stage II/III, 7% (n=4) were resected stage IV, 4% (n=2) were unresectable stage III in remission, and 14% (n=8) were unresectable stage IV in remission. Melanoma primaries included: 82% (n=46) cutaneous, 7% (n=4) mucosal, 5% (n=3) uveal, 5% (n=3) unknown. ctDNA was detected in 30 out of 56 patients with confirmed recurrence/relapse, with an overall sensitivity of 53.6%. Sensitivity varied by site of recurrence/relapse. Sensitivity for ctDNA detection of brain mets was 33.3% (4/12); skin/mucosa/muscle recurrence or mets was 37.5% (6/16); lung mets was 61.5% (8/13); bone mets was 75% (3/4); liver mets was 87.5% (7/8), and lymph node mets was 87.5% (14/16). The odds of detecting ctDNA at relapse or recurrence were significant amongst patients with lymph node mets (OR=10.5, 95% CI 2.10-52.58, p=0.004) and patients with multiple anatomic sites (2+) of mets (OR=7.61, 95% CI 1.27-66.67, p=0.032). **Conclusions:** ctDNA monitoring shows potential in detecting recurrence or relapse in patients with melanoma. We found that location of metastatic disease impacts the shedding of ctDNA and its detection of macroscopic disease. Larger studies are needed to refine the role of ctDNA monitoring and its clinical application in melanoma surveillance. Research Sponsor: Clinical and Translational Science Award (CTSA); UL1TR002373.

9585 Poster Session

Multiomic analysis of cutaneous squamous cell carcinoma (cSCC) and association with response to anti-PD1 therapy (PD1).

Yu-Ju Kuo, Tuba Nur Gide, Yizhe Mao, Nurudeen A. Adegoke, Thomas Bennett, Alexander M. Menzies, Georgina V. Long, James S. Wilmott, Ines Esteves Domingues Pires da Silva; Melanoma Institute Australia, The University of Sydney, National Taiwan University Hospital Hsin-Chu Branch, Sydney, Australia; Melanoma Institute Australia, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, and Blacktown Hospital, Sydney, Australia

Background: PD1 induces a durable response and improves the survival of patients (pts) with advanced cSCC; however, about 40% of pts are resistant to this treatment. Multiomic analysis (e.g., tumor mutational burden [TMB] and gene expression profiling [GEP]) has shown predictive value for PD1 response in various cancer types. This study aims to perform multiomic analysis of cSCC and study its association with the response to PD1. **Methods:** cSCC pts were prospectively enrolled in the PIP-PREDICT study (NCT06536257). Baseline tumor tissues were sent for: a) targeted TSO500 DNAseq (NGS), for TMB and mutational status, and b) NanoString Pancancer 360IO, for GEP. Baseline characteristics and clinical outcomes were collected. Pts treated with PD1 were categorized as responders (complete/partial response) or non-responders (progressive disease) based on RECIST 1.1. Pts with stable disease were further categorized into responders/ non-responders based on PET response (PERCIST). **Results:** 26 cSCC pts were enrolled; the median age was 79 (range 39-98) and 73% (n=19) were male. 7 pts (27%) were immunocompromised and 4 were on immunosuppressants. Head and neck (HN) primaries were present in 54% (n=14), and 58% (n=15) of the pts had stage IV disease. NGS was performed on 21 pts, revealing a median TMB of 39.2 mut/Mb (range 17.3-122.2). TP53 mutations were present in all cases (100%), with other frequent mutations observed in CDKN2A (43%), TERT promoter (43%), FAT1 (38%), NF1 (24%), PIK3CA (24%), TGFBR2 (19%), and CREBBP (19%). GEP of 22 pts showed that cSCC with HN primaries exhibited higher cancer-associated fibroblast (p=0.018) and stromal (p=0.035) signatures (sig), compared to non-HN pts. Pts on immunosuppressants demonstrated lower expression of cytokine (p=0.031), effector cell (p=0.019), and NK cytotoxicity (p=0.0498) sig compared to those not on immunosuppressants. 18 pts received PD1 for advanced cSCC with evaluable disease; ORR was 61.1% and DCR was 72.2%. After a median follow-up of 12.4 months (95% CI, 4.1-20.7), the 12-months PFS and OS rates were 57.9% and 94.7%, respectively (the median PFS and OS were not reached). Responders to PD1 exhibited higher expression of MHC-I (p=0.003), T cells (p=0.039), NK cells (p=0.009), interferon-gamma (p=0.03), cell adhesion molecules (p=0.039), and antigen presentation (p=0.03) sig. Conversely, non-responders showed higher levels of angiogenesis (p=0.005), endothelium (p=0.005), hypoxia (p=0.039), and CCR8 (p=0.017) sig. No differences were observed in the expression of immune checkpoints (e.g. PD-1, LAG3), TMB, or specific mutations in responders vs. non-responders. **Conclusions:** cSCC responsive to PD1 have higher expression of immune sig and lower expression of stromal and hypoxic sig. Well-known predictive features of response to immunotherapy (e.g. TMB, PD-1 sig) were not associated with response in this cohort. Research Sponsor: None.

9586 Poster Session

Immunoembolization for patients with uveal melanoma hepatic metastasis: A single-institution real-world data analysis.

Rino S. Seedor, David J. Eschelman, Carin F. Gonsalves, Robert D. Adamo, Marlana M. Orloff, Erin Sharpe-Mills, Madeleine Naccarato, Alexandre J. Motta, Alexander Blackley, Aurora Mills, Takami Sato; Sidney Kimmel Comprehensive Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: Metastatic disease occurs in up to 50% of patients with uveal melanoma (UM) despite successful treatment of the primary eye tumor. The liver is the predominant organ of involvement in more than 90% of patients, and control of liver metastases is essential to prolonging overall survival (OS). Immunoembolization (IE) with granulocyte-macrophage colony-stimulating factor +/- interleukin-2 is considered a 1st line liver-directed therapy for those with <50% hepatic tumor burden at our institution. It is well tolerated, has limited side effects, no cumulative toxicities, and affords good quality of life between scheduled treatments. **Methods:** A retrospective single-institution chart review was performed on consecutive series of metastatic UM (MUM) patients with hepatic metastasis who were treated at Thomas Jefferson University with IE treatment. The following data were collected from medical records: age, gender, IE treatment history, treatment history before and after IE, last follow-up date, and date of death. **Results:** 604 MUM patients (median age 62, range 19-91) received IE treatment for UM hepatic metastasis from 11/2000 to 01/2025 for a total of 3,715 IE treatments. 22 patients continue to receive IE. Patients received a median of 4 IE treatments (range 1-45) over 4 months (range 1-118 months). With a median follow-up of 18.3 months (range 0.1-176.4), median OS after IE treatment initiation was 20.0 months (95%CI 18.2-22.3). OS was 73.2% at 1 year, 41.8% at 2 years, 25.3% at 3 years, and 11.2% at 5 years. 30% of patients had treatment of metastatic disease prior to IE and 83% had treatment after IE. 134 patients (22%) had concurrent therapy with IE, most commonly checkpoint inhibitor therapy (48%). Median OS was 21.5 months (95%CI 18.9-23.4) for patients who received IE as first-line metastatic therapy. Except for one patient who died of takotsubo cardiomyopathy after the first IE treatment, IE treatments were well tolerated without serious or long-term complications. Of the subset of patients that experienced a prolonged OS of ≥3 years with IE (n=117), they received a median of 10 treatments over 16 months. Of the patients with prolonged OS of ≥5 years with IE (n=33), they received a median of 12 treatments over 19 months. Patients that experienced prolonged OS with IE ≥3 years were more likely to be female (69%). The longest patient treated with IE was a female who received 45 IE treatments over 10 years. **Conclusions:** We conducted the largest retrospective study of MUM patients who have received IE treatment. Our real-world data indicates that IE is a safe and effective liver-directed therapy for UM hepatic metastases, and IE should be considered a mainstay of treatment for patients with limited hepatic tumor burden. Research Sponsor: None.

9587 Poster Session

Real-world outcomes of immunosuppressed patients with Merkel cell carcinoma treated with immune checkpoint inhibitors.

William J Mullally, Andrew Scott Brohl, Aisha Ghaus, Mark J. Shackleton, Yang Wang, Shahneen Sandhu, Jurgen Becker, Marcin Dzienis, Liam Dwyer, Jenny H.J. Lee, Adnan Khattak, Lydia Warburton, Christopher Steer, Wen Xu; Department of Medical Oncology, Princess Alexandra Hospital, Brisbane, QLD, Australia; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Department of Medical Oncology, The Alfred Hospital, Melbourne, VIC, Australia; Department of Oncology, Alfred Health and Monash University, Melbourne, Australia; Department of Medical Oncology, Melbourne, VIC, Australia; Department of Medical Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia; University Hospital Essen, German Cancer Consortium (DKTK), Partner Site Essen/Düsseldorf, German Cancer Research Center (DKFZ), Heidelberg, Germany; Department of Medical Oncology, Southport, QLD, Australia; Chris O'Brien Lifehouse, Camperdown, NSW, Australia; Macquarie University, Sydney, Australia; Hollywood Private Hospital, Perth, Western Australia, Australia; Fiona Stanley Hospital, Edith Cowan University, Perth, Western Australia, Australia; Border Medical Oncology, Albury, NSW, Australia; University of Queensland, Bisbane, QLD, Australia

Background: Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer that disproportionately affects older adults & the immunosuppressed. Immune checkpoint inhibitors (ICI) are highly effective in advanced MCC (aMCC), but pivotal ICI trials excluded immunosuppressed patients, highlighting an unmet need for this cohort. **Methods:** Clinical databases from 10 centers across 3 countries, were retrospectively analysed to identify immunosuppressed patients with aMCC who have received ICI. These patients were categorized into solid organ transplant (SOT), human immunodeficiency virus (HIV), hematological malignancies (HM) & autoimmune (AI) diseases. The overall aim was to assess treatment outcomes in patients excluded from trials. **Results:** This retrospective multicenter study identified 46 immunosuppressed patients (80% male) with aMCC and treated with ICI. The median age was 72 years (Table 1). The objective response rate (ORR) to anti-PD1/PDL1 ICI was 47.8%, with median progression-free survival (PFS) & overall survival (OS) of 23.4 & 40.9 months, respectively. 56.5% of patients have died at data cutoff. Cause of death included MCC (69.2%), comorbidities/others (15.4%), hematological malignancies (11.5%), and ICI-pneumonitis (3.9%). There were no deaths from graft failure, AI diseases or HIV. 8.7% developed ≥ grade 3 ICI-related adverse event (irAE). There was no difference in ORR (44% vs. 40%), OS (43.6 vs. 40.5 months, p = 0.68) or PFS (26.7 vs. 22.6 months, p = 0.18) in patients who experienced any grade irAE compared to those who did not. Clinicians were less likely to offer first line ICI to SOT patients (60%), particularly non-renal SOT patients 50%, compared with non-SOT immunosuppressed patients (89%). SOT patients had numerically lower response rates vs. non-SOT patients (ORR 30% vs 56%), significantly shorter PFS & OS at 6.5 months vs. 34.6 months (p= 0.001) & 13.1 months vs. 47.6 months (p = 0.002), respectively. **Conclusions:** Real world data shows that immunosuppressed MCC patients derive significant clinical benefit from ICI with acceptable rates of irAEs. Majority of immunosuppressed MCC patients (69%) died of disease progression, with 3.9% dying from an irAE & 11.5% from deterioration in HM. This suggests pre-existing immunosuppression should not significantly deter the use of ICI in patients with MCC. Patients with SOT have worse outcomes when treated with ICI compared with other immunosuppressed groups. Clinicians were more likely to reserve ICI use beyond first line. Research Sponsor: None.

Study cohort.

	SOT (n=10)	HIV (n=4)	Autoimmune disease (n=16)*	Hematological malignancy (n=16)
Median Age (Range)	72 (18-90)			
Male, n (%)	37 (80)			
ORR (%)	30	100	56	38
Use of ICI First Line (%)	60	100	81	94
PFS months (95% CI)	6.5 (0.6 – 12.5)	41.1 (15.4 – 66.8)	34.9 (13.3 – 56.5)	20.8 (8.1 – 33.5)
OS months (95% CI)	13.1 (2.3 – 24.0)	Not reached	44.2 (22.8 – 65.5)	39.1 (23.4 – 54.8)

*15 on treatment.

9589 Poster Session

Tobacco smoking as a risk for cutaneous squamous cell carcinoma in skin of color.

Tahira Naqvi, Nolan Holley, Michael Kolodney, Joanna Amy Kolodney; WVU Medicine, Morgantown, WV; West Virginia University, Department of Internal Medicine, Morgantown, WV; West Virginia University Department of Dermatology, Morgantown, WV; West Virginia University, Morgantown, WV

Background: Ultraviolet radiation (UVR) along with immunosuppression, tobacco smoking and age are the major risk factor cutaneous squamous cell carcinoma (cSCC) in White individuals. However, the risk factors for cSCC in skin of color (SOC), where UVR may be less important, remain inadequately explored. **Methods:** A retrospective cohort study of real-world aggregate patient data from the TriNetX global federated research network was used to identify patients with cSCC. Cohorts were created for Asian, Black/African American, White/Caucasian, and Hispanic patients with ICD-10 codes for cSCC. These cohorts were then 1:1 propensity matched with a control group of the same race/ethnicity with ICD-10 codes for benign skin lesions. Propensity matching was performed for age at cSCC diagnosis and patients' sex. The number of patients in the smokers in the cSCC group was then compared to the number of smokers in the control group. **Results:** We identified 2122 Asian subjects, 5237 Black subjects, 4256 Hispanic subjects and 227,683 White subjects with cSCC. We also identified a control cohort of each race/ethnicity with a diagnosis of benign neoplasm of the skin. After propensity matching for age at diagnosis and sex, White subjects diagnosed with cSCC were 2.3 fold more likely to have a previous history of cigarette smoking than White subjects with the control diagnosis ($P<0.001$). When looking at SOC, Black subjects were 3.3 fold ($p<0.001$), Asians 3.6 were fold ($p<0.001$), and Hispanics were 2.5 fold ($p<0.001$) more likely to have a cigarette smoking diagnosis than subjects of the same race with the control diagnosis. **Conclusions:** This study suggests that smoking is a major risk factor in for cSCC in SOC. These findings emphasize this importance of tailored preventative strategies to address disparities in tobacco smoking behaviors. Future research should seek to further elucidate the underlying socioeconomic, cultural, and health-care access factors contributing to differences for optimization of equitable care. Research Sponsor: None.

9590 Poster Session

Independent validation of a 16-protein test to assess malignant potential of small uveal melanocytic tumors.

David Alan Reichstein, Julia Litvinov, Olga Zolochevska, Kyle R. Covington, Amy Schefler, Zelia M. Correa, Jason Maarsingh, Kasia Wozny, Katherina Alsina, J. William Harbour; Tennessee Retina, Nashville, TN; Castle Biosciences, Inc., Friendswood, TX; Castle Biosciences, Friendswood, TX; Retina Consultants of Texas, Bellaire, TX; University of Miami Bascom Palmer Eye Institute, Miami, FL; Castle Biosciences, Phoenix, AZ; UT Southwestern Medical Center, Dallas, TX

Background: Uveal melanocytic tumors of indeterminate malignant potential (UMTIMP) are usually managed by a "watch and wait" approach before the decision to treat. Although the aggressiveness of these lesions can be assessed by tumor-biopsy based molecular testing, serial tumor biopsies may be impractical and not always feasible for routine clinical management of UMTIMPs. In contrast, aqueous humor (AH) sampling can be safely performed as an outpatient procedure and is repeatable. AH protein biomarkers strongly associated with aggressive UM could be used as a sensitive and objective biological marker of malignant transformation, facilitating earlier tumor biopsy and treatment when clinically indicated. The purpose of this study was to validate a previously developed 16-protein algorithmic test for identification of high-risk tumor biology in AH sample. **Methods:** All study participants were clinically diagnosed with UM and had the 15-GEP, PRAME and 7-gene UM panel next-generation sequencing (NGS) test results available. AH samples (N=71) were prospectively collected at 3 independent sites under IRB approved protocols. The samples were analyzed with the Olink Target 96 Oncology II panel. The low-risk group included Class 1 and BAP1 wild type samples, and the high-risk group included Class 1 BAP1-mutant samples and all Class 2. Algorithmic analyses were performed in R and demographics analysis was performed in GraphPad Prism (version 10). **Results:** The sample distribution was representative of a typical UM patient cohort: average age was 62.4±15.1 years, tumor diameter 11.16±3.56 mm, and tumor thickness 4.85± 2.94 mm. The 15-GEP identified 48/71 of tumors as Class 1, and 23/71 tumors as Class 2. There was a significant difference in tumor diameter (P=0.003) and tumor thickness (P=0.001) between Class 1 and Class 2 patients. The proteins primarily belonged to Signal Transduction, Disease, and Cytokine Signaling pathways, based on Olink's Pathway Browser. The 16-protein test had a sensitivity of 92%, specificity 52%, NPV 92%, and PPV 51%. **Conclusions:** A novel 16-protein algorithmic test for predicting high-risk tumor biology of the uveal melanocytic lesions was independently validated in a multi-center study. This high sensitivity test would help to accurately identify high-risk melanocytic lesions based on AH sample and provide a clinically useful ancillary approach for guiding decisions for definitive tumor biopsy and treatment. Research Sponsor: None.

9591 Poster Session

PD-1–directed intratumoral immunotherapy for cutaneous carcinomas: Interim results from an ongoing study of INTASYL PH-762.

Mary C Spellman, Katharine Furst, Linda Mahoney; Panclarity LLC, San Francisco, CA; Prosoft Clinical, Chesterbrook, PA; Phio Pharmaceuticals Inc., Marlborough, MA

Background: Immune checkpoint-targeted antibodies directed at PD-1 or PD-L1 block co-inhibitory receptors expressed by anti-tumor T cells, breaking immune tolerance against tumor cells and generating cancer immunity. PH-762 is an INTASYL compound designed to precisely silence PD-1 mRNA. INTASYL is a patented, self-delivering RNAi technology designed to impart specific properties to small interfering RNAs. PH-762's unique structural and chemical modifications ensure an optimized cell and tissue uptake profile with intratumoral (IT) administration. Local delivery of immunotherapy minimizes systemic exposure and off-target toxicities and may decrease tumor size and improve surgical morbidity. The efficient uptake of PH-762 by human T cells, silencing of PD-1 mRNA and subsequent protein reduction has been demonstrated preclinically. Murine-targeted PH-762 (mPH-762) injections are able to silence PD-1 mRNA in T cells within the murine tumor and increase the secretion of IFN-γ. **Methods:** This open-label Phase 1 clinical study (NCT 06014086) is designed to evaluate the safety and tolerability of neoadjuvant use of IT PH-762 in cutaneous squamous cell carcinoma, melanoma, or Merkel cell carcinoma, to determine the pharmacokinetic profile of PH-762 after IT injection, to observe pathologic and immunologic tumor responses, and to determine the recommended dose for development. Escalating dose concentrations of PH-762 (from 1.14 mg/mL through 22.00 mg/mL) are tested serially in cohorts of 3 patients each. Patients receive IT PH-762 once weekly, 4 times over a 3-week period prior to surgical excision, which occurs 5 weeks after the initial injection. Tumor changes are evaluated per iRECIST criteria and pathological response. **Results:** Seven patients in two dose cohorts have received IT PH-762 (1.14 or 2.39 mg/mL). No dose-limiting toxicities or serious adverse events have been reported. Pathologic response was reported following surgical excision of the tumor (or tumor site). Of the 6 patients with SCC, 2 had complete response, 2 had partial response (1 near complete with <10% viable tumor), and 2 were non-responders. One patient with metastatic melanoma had no response. **Conclusions:** IT PH-762 has been well tolerated, with no evident safety signals or reported systemic or off-target toxicities, and dose escalation has resumed per protocol. Clinical and histologic evidence of tumor response is encouraging. PH-762 may decrease tumor bulk or provide a non-surgical alternative in specific circumstances, while minimizing systemic exposure and off-target toxicities. Clinical outcomes, coupled with pharmacokinetic and immunologic response data will inform continued clinical development of PH-762. Clinical trial information: 06014086. Research Sponsor: Phio Pharmaceuticals.

TPS9592 Poster Session

Phase I/Ib study of concurrent intravenous (IV) and intrathecal (IT) nivolumab (N) and relatlimab (R) for metastatic melanoma (MM) patients (pts) with leptomeningeal disease (LMD).

Isabella Claudia Glitza, Suzanne Phillips, Ida John, Roland L. Bassett Jr., Michelle L. Rohlfs, Jessie Richard, Masood Iqbal, Ian E. McCutcheon, Sherise D. Ferguson, Jeffrey S. Weinberg, Golnaz Morad, Adi Diab, Rodabe Navroze Amaria, Jennifer Leigh McQuade, Alexandra Ikeguchi, Hussein A. Tawbi, Elizabeth M. Burton, Michael A. Davies; University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pts with LMD face dismal prognosis, with median overall survival (OS) measured in months. We previously reported the safety and efficacy data from an open label, single arm and center phase I/IB trial for MM pts with LMD, using IT/IV N (*Nature Medicine*, Glitza et al.). 50 pts were treated. Median OS was 7.5 months and the toxicity was minimal. This approach was adopted into the NCCN guidelines, as these data suggest a subset of pts benefit from IT/IV N without high toxicity. N (anti-PD1) and R (anti-LAG3) represents a fixed- dose combination (FDC) approved by the FDA in 2022 for the treatment of unresectable MM. IV N/R has shown improved outcomes vs N in MM pts, and we identified LAG3 expression on CD8 T cells in the cerebrospinal fluid (CSF) of MM pts with LMD, in a pattern very similar to the expression of PD1. Subsequent work on C57BL/6 murine models with B16 and YUMM3 established LMD confirmed that combined treatment with IT/systemic anti-PD1/anti-LAG3 was the only treatment to significantly improve OS versus IT/systemic control treatment. We therefore added a non-randomized arm of concurrent IT/IV N/R to the previous study. Based on the prior tolerated dose of IT N 50mg, and the approved FDC ratio for IV N/R, we chose a FDC of IT N/R 50mg/16.7mg with concurrent with IV N/R at 480mg/160mg. We hypothesize that IT/IV N/R will be safe and an effective treatment for MM pts with LMD. **Methods:** This is a Phase Ib, non-randomized, single center trial of concurrent IT/IV N/R in adult (≥18 years) MM pts with LMD (NCT03025256). Up to 20 pts will receive IT N/R every 28 days, and Cycle 1 (C1) will consist of IT N/R only. In subsequent cycles the IT dose will be followed by an IV dose of N/R. Most pertinent inclusion criteria are radiographic and/or CSF cytological evidence of LMD, ECOG PS of ≤ 2, ≤ 4 mg per 24 hours of dexamethasone (or the equivalent), with adequate organ function. Prior radiation and treatment with immunotherapy is allowed, as is the use of concurrent BRAF/MEK inhibitors. Primary endpoint is safety, and Bayesian toxicity monitoring rule will be used. Secondary endpoints are OS, survival rates at 3,6 and 12 months, and median duration of treatment. CSF, blood and microbiome samples will be collected at various time points. The first patient was enrolled in October 2024 and accrual of patients is ongoing (NCT03025256). Clinical trial information: NCT03025256. Research Sponsor: Bristol Myers Squibb.

TPS9593 **Poster Session**

Phase I/IIa dose finding study of triplet regimen of relatlimab (RELA), ipilimumab (IPI), and nivolumab (NIVO) in first-line therapy of metastatic melanoma (TRINITY).

Elizabeth M. Burton, Tara Marie Davidson, Krysta McVay, Denai R. Milton, Rodabe Navroze Amaria, Isabella Claudia Glitza, Jennifer Leigh McQuade, Theresa H. Nguyen, Alexandra Ikeguchi, Adi Diab, Weiyi Peng, Michael A. Davies, Hussein A. Tawbi; Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Houston, Houston, TX

Background: NIVO (anti-PD1) alone or in combination with IPI (anti-CTLA-4) or RELA (anti-LAG3) are approved immune checkpoint blockade (ICB) agents for the treatment (tx) of patients (pts) with advanced, unresectable metastatic melanoma. Doublet combinations induce higher rates of durable disease control vs single agent, translating into nominal improvements in survival. While there is no established dose-response relationship for NIVO alone or with RELA, IPI at higher doses induces higher objective response rate (ORR) but increased grade ≥3 immune-related adverse events. Deeper mechanistic understanding points towards potential synergy given IPI's role in expanding the TCR repertoire and modulating suppressive T cell populations while NIVO+RELA regulate the exhaustion signatures of activated T cells and allow for improved effector function. Recently, results from RELATIVITY-048 combining all three ICB agents (NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W) demonstrated impressive efficacy with high response rates (59% ORR) and seemingly improved progression free and overall survival (PFS, OS) over previously reported doublet regimens. This study evaluated a markedly lower IPI dose than the approved regimen and did not include a dose escalation component to optimize the IPI dosing strategy. Our team seeks to optimize the dose and schedule of IPI to combine with NIVO+RELA in order to determine the recommended phase II dose (RP2D) for triplet ICB and maximize clinical benefit while maintaining a toxicity profile comparable to approved regimens. **Methods:** In this single center, investigator initiated, phase I/IIa study evaluating triplet ICB (NCT06683755), all pts will receive FDA approved regimen of NIVO 480mg + RELA 160mg IV Q4W along with escalating doses of IPI . Dose escalation (DE) with IPI will begin at 0.5mg/kg Q4W 4 induction doses and will incrementally escalate up to 2mg/kg Q4W. Maintenance tx will consist of NIVO+RELA Q4W. Bayesian optimal interval (BOIN) design will be used to identify the maximum tolerated dose (MTD) and RP2D (primary objective) in the DE portion, accruing an estimated 12-18 pts. The PhIIa portion will accrue an additional 12-18 pts at the RP2D to better characterize safety, and determine the ORR, (primary objective) by RECIST 1.1. Secondary objectives include PFS, OS, and tumor and immunological correlatives obtained on pre and post tx blood and tumor samples. Pts must be previously untreated, unresectable, or advanced melanoma. Non IPI containing prior adjuvant or neo-adjuvant tx will be permitted if the last dose has been >6 months. Pts with asymptomatic brain metastasis are allowed, provided no immunesuppressive doses of corticosteroids are required. Safely biopsiable lesions are required for pts enrolled in the PhII portion. This study is open for accrual at MD Anderson Cancer Center in Houston, Texas. Clinical trial information: NCT06683755. Research Sponsor: BMS.

TPS9594 **Poster Session**

A multicenter, randomized, controlled, open-label, phase 2 study of the PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein IBI363 in mucosal and acral melanoma.

Bin Lian, Yu Chen, Zhiguo Luo, Xiaoshi Zhang, Di Wu, Ke Li, Zhengyun Zou, Meiyu Fang, Chen Jing, Huijing Feng, Yu Jiang, Weizhen Zhang, Xianan Li, Renbing Jiang, Enwen Wang, Cuihua Yi, Yinbin Zhang, Xueying Zhang, Xiubao Ren, Jun Guo; Peking University Cancer Hospital & Institute, Beijing, China; Fujian Cancer Hospital, Fuzhou, China; Fudan University Shanghai Cancer Center, Shanghai, China; Sun Yat-Sen University Cancer Center, Guangzhou, China; The First Hospital of Jilin University, Changchun, China; Yunnan Cancer Hospital, Kunming, China; Nanjing Drum Tower Hospital, Nanjing, China; Zhejiang Cancer Hospital, Hangzhou, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Shanxi Bethune Hospital, Taiyuan, China; West China Hospital of Sichuan University, Chengdu, China; The Third People's Hospital of Zhengzhou, Zhengzhou, China; Hunan Cancer Hospital, Changsha, China; Affiliated Tumor Hospital of Xinjiang Medical University, Urumchi, China; Chongqing University Cancer Hospital, Chongqing, China; Qilu Hospital of Shandong University, Jinan, China; The Second Affiliated Hospital of Xi'an Jiaotong University, Xian, China; Jilin Cancer Hospital, Changchun, China; Tianjin Cancer Hospital, Tianjin, China

Background: Although several immune checkpoint inhibitors have been approved for advanced melanoma, there remain significant unmet clinical needs, particularly for immune-cold subtypes such as mucosal and acral melanoma, which are frequently observed in Chinese patients (pts). IBI363 targets and activates tumor-specific T cells that express both PD-1 and IL-2Rα, leading to enhanced antitumor activity and reduced toxicity. Previous phase 1 studies of IBI363 reported manageable safety profiles with encouraging efficacy in advanced melanoma (2024 ASCO Annual Meeting [9562], ESMO Virtual Plenary [VP4-2024], SITC [1502]). Here, we present the trial in progress of a phase 2 study evaluating efficacy and safety of IBI363 monotherapy versus pembrolizumab in mucosal and acral melanoma. **Methods:** This multicenter, randomized, controlled, open-label, phase 2 study planned to enroll 180 pts. Main inclusion criteria are: 1) locally advanced unresectable or metastatic mucosal or acral melanoma; 2) no previous systemic treatment for melanoma; 3) at least one measurable tumor lesion (target lesions) per RECIST v1.1. Pts with active or symptomatic central nervous system metastasis are excluded. Pts are randomized in a 1:1 ratio to receive IBI363 1 mg/kg Q2W (with a priming dose of 100 μg/kg administered 7 days before the full dose) in the experimental arm or to receive pembrolizumab 200 mg Q3W in the control arm. Stratification factors include subtype (mucosal vs acral) and M staging (M0 vs M1a(0)/M1b(0) vs M1a(1)/M1b(1) or M1c/M1d, (0) indicating baseline lactate dehydrogenase [LDH] $\leq$ upper limit normal [ULN] and (1) indicating baseline LDH $>$ ULN). The primary endpoint is progression-free survival (PFS) assessed by independent radiological review committee (IRRC) per RECIST v1.1. The secondary endpoints include investigator-assessed PFS, IRRC-assessed and investigator-assessed objective response rate (ORR), disease control rate (DCR), duration of response (DoR), time to response (TTR) per RECIST v1.1, overall survival (OS), safety, pharmacokinetics (PK) and immunogenicity. No interim analysis is planned. A total of 118 PFS events among 180 pts is estimated to demonstrate the superior efficacy of IBI363 compared to the control, with a power of 90% (α=0.025, one-sided). Clinical trial information: CTR20250280. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

TPS9595 **Poster Session**

NivoReach: Integrated study to demonstrate similarity of JPB898 to reference nivolumab in combination with ipilimumab in patients with advanced melanoma.

Piotr Rutkowski, Dimitrios Bafaloukos, Andreia Cristina De Melo, Claudia Hemmelmann, Samik Banerjee, NivoReach Investigators; Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; First Oncology Department, Metropolitan Hospital, Athens, Greece; Brazilian National Cancer Institute (INCA), Rio De Janeiro, Brazil; Sandoz AG, Holzkirchen, Germany

Background: JPB898 is being developed as a biosimilar to reference nivolumab. Analytical and functional in vitro similarity of JPB898 to reference nivolumab has been demonstrated. NivoReach will assess the pharmacokinetic (PK) and efficacy similarity of JPB898 to reference nivolumab in patients with untreated advanced melanoma. Induction therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg is approved for advanced melanoma, before nivolumab maintenance therapy. However, the unfavorable toxicity profile of this regimen, attributed mainly to ipilimumab, has led to investigation of alternative regimens. The Phase IIIb/IV CheckMate 511 trial compared the approved regimen with an "inverse dosing" regimen comprising nivolumab 3 mg/kg and ipilimumab 1 mg/kg. Similar response and overall survival rates were observed between the treatment groups, as well as a lower incidence of immune-related toxicities and a lower rate of discontinuation due to treatment-related adverse events with the inverse regimen versus the approved regimen (Lebbé C, et al. J Clin Oncol 2019;37: 867–75). Therefore, inverse dosing is an appealing combination regimen for use in NivoReach, providing a treatment option with a more favorable risk–benefit ratio to a broader advanced melanoma patient population versus the approved regimen. Currently, the study is approved in 19 countries, including the USA and some EU member states. **Methods:** This global, randomized, double-blind, parallel-group study is recruiting participants with untreated, unresectable Stage III or metastatic Stage IV melanoma, measurable per RECIST v1.1. Participants must have an ECOG performance status ≤1. Participants will not be eligible if they have active brain metastases, ocular melanoma, or other active malignancy that is untreated or requires concomitant systemic therapy. Eligible participants will be randomized 2:1:1 to JPB898, or US-licensed or EU-authorized nivolumab, in combination with ipilimumab. Randomization will be stratified by *BRAF* V600 mutation status, PD-L1 expression status, and metastasis stage. In the 12-week induction phase, participants will receive 4 cycles of the inverse regimen (nivolumab 3 mg/kg + ipilimumab 1 mg/kg, Q3W). In the maintenance phase, participants will receive fixed-dose monotherapy (480 mg, Q4W) with JPB898 or reference nivolumab from Week 16 to 48. The co-primary PK endpoints are area under the serum concentration–time curve (AUC) after the first dose and AUC after the fourth dose in the induction phase. The primary efficacy endpoint is best overall response (complete or partial response) up to 28 weeks. Other PK, efficacy, safety, and immunogenicity endpoints will also be assessed up to 52 weeks. The planned randomized sample size is 720 participants. Clinical trial information: NCT06587451. Research Sponsor: Sandoz.

TPS9596 Poster Session

A randomized phase 2 peri-operative (neoadjuvant plus adjuvant) study of fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus anti–PD-1 alone in patients with resectable stage III and IV melanoma.

Rodabe Navroze Amaria, Axel Hauschild, Michael Lowe, Janis M. Taube, Adil Daud, Thach-Giao Truong, Sarah A. Weiss, Ankit Mangla, Tapan Miyani, Deidre Williams, Fang Fang, Shuquan Chen, Mark Salvati, Israel Lowy, Rossella Marullo, Matthew G. Fury, Karl Lewis, Humberto Lara-Guerra; The University of Texas MD Anderson Cancer Center, Houston, TX; University Hospital Schleswig-Holstein, Kiel, Germany; Emory University, Atlanta, GA; Johns Hopkins University, Baltimore, MD; University of California San Francisco, San Francisco, CA; Cleveland Clinic, Cleveland, OH; Rutgers Cancer Institute, New Brunswick, NJ; University Hospitals Seidman Cancer Center, Cleveland, OH; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Prior studies demonstrated use of neoadjuvant plus adjuvant immune checkpoint inhibitors (ICIs) improves event-free survival (EFS) compared with upfront surgery and adjuvant ICI therapy alone, supporting that peri-operative (neoadjuvant plus adjuvant) ICI therapy improves survival outcomes in patients (pts) with clinical stage III and resectable IV melanoma (Mel). Initial efforts in Mel trials to explore combined blockade by anti-programmed cell death-1 (anti–PD-1) and anti-lymphocyte activation gene 3 (anti–LAG-3) antibodies produced incrementally better efficacy than blockade of the PD-1 pathway alone. However, these efforts may not have provided optimal blockade of the two pathways. We have utilized VelocImmune technology to create potentially best-in-class, high-affinity, fully human immunoglobulin G4-blocking antibodies, fianlimab (FIAN; anti–LAG-3) and cemiplimab (CEMI; anti–PD-1). In a multicohort study (NCT03005782), FIAN + CEMI demonstrated reproducibly high clinical activity (objective response rate [ORR]: 57%; median progression-free survival: 24 months; N=98) in three independent cohorts of pts who were naïve to anti–PD-1 treatment in the advanced Mel setting, with an acceptable safety profile. Thus, the combination of FIAN + CEMI warrants an investigation as a peri-operative regimen in resectable, clinically detectable, high-risk, stage III and IV cutaneous Mel. **Methods:** This is a randomized Phase 2 peri-operative study (NCT06190951) in pts with clinical stage III/IV Mel with resectable disease. Pts will receive 3 cycles of neoadjuvant therapy followed by complete surgical resection, and continue with an optional 15 cycles of adjuvant therapy, based on pathological response. The primary objective is to compare the effect of FIAN + CEMI versus CEMI alone as measured by the pathological complete response (pCR) rate. Approximately 150 pts will be randomized 1:1:1 to three arms (intravenously once every 3 weeks): Arm A, CEMI 350 mg + placebo; Arm B, High Dose FIAN + CEMI 350 mg; Arm C, Low Dose FIAN + CEMI 350 mg. Pts will be stratified based on tumor, node, metastasis (TNM) stage and geographical region. Key inclusion criteria: age ≥18 years; resectable clinical stage III/IV histologically confirmed Mel; pts with stage III Mel must have clinically detectable disease; Eastern Cooperative Oncology Group performance status 0 or 1; adequate bone marrow, hepatic, and kidney function. The primary endpoint is pCR rate by blinded independent pathological review performed centrally. The secondary endpoints are pCR rate (by local assessment), major pathological response (by local and central review), EFS, overall survival, distant metastasis-free survival, relapse-free survival, ORR, safety, pharmacokinetics, immunogenicity, and patient-reported outcomes. Clinical trial information: NCT06190951. Research Sponsor: Regeneron Pharmaceuticals, Inc.; NA.

TPS9597 Poster Session

A randomized, phase 2/3 clinical trial investigating RP2 plus nivolumab vs ipilimumab plus nivolumab in immune checkpoint inhibitor-naïve patients with metastatic uveal melanoma.

Joseph J Sacco, Justin C. Moser, Allison Betof Warner, Ryan J. Sullivan, Diwakar Davar, Alexander Noor Shoushtari, Richard D. Carvajal, Sapna Pradyuman Patel, Anthony M. Joshua, Jessica Cecile Hassel, Mark Navarro, Rahul Marpadga, Giuseppe Gullo, Marlana M. Orloff; The Clatterbridge Cancer Centre and University of Liverpool, Wirral and Liverpool, United Kingdom; HonorHealth Research Institute, Scottsdale, AZ; Stanford Medicine, Stanford, CA; Massachusetts General Hospital, Boston, MA; UPMC Hillman Cancer Center, Pittsburgh, PA; Memorial Sloan Kettering Cancer Center, New York, NY; Northwell Health Cancer Institute, New Hyde Park, NY; University of Colorado Comprehensive Cancer Center, Aurora, CO; UNSW Sydney, Sydney, Australia; University Hospital Heidelberg, Heidelberg, Germany; Replimune, Inc., Woburn, MA; Thomas Jefferson University Hospital, Philadelphia, PA

Background: Uveal melanoma (UM) is the most common primary intraocular malignancy, accounting for nearly 90% of ocular melanomas and up to 5% of melanomas overall. Approximately 50% of patients (pts) with UM will develop metastatic disease, with the liver being the most common site of metastases (~90%). The prognosis for pts with metastatic UM (mUM) is poor, with a median overall survival (OS) of approximately 1 year. Effective treatment options for mUM are limited as it responds poorly to single-agent immune checkpoint inhibitors (ICIs; <10% response rate). Response rates are slightly higher with combination therapies (12%–18%), but often at the expense of increased toxicity. Tebentafusp is FDA approved for mUM based on survival benefit; however, its use is restricted to pts who are HLA-A*02:01 positive, and only ~10% of pts achieve an objective response. RP2 is a selectively replication-competent herpes simplex virus type 1–based oncolytic immunotherapy expressing GM-CSF, a fusogenic glycoprotein (GALV-GP-R–), and an anti–CTLA-4 antibody-like molecule. Prior phase 1 preliminary clinical data of RP2 as monotherapy or in combination with nivolumab (nivo) demonstrated a promising safety profile and anti-tumor activity with an ORR of 29.4% in 17 patients with mUM, most of whom had received prior ICIs. This study will assess the efficacy and safety of RP2 + nivo vs ipilimumab (ipi) + nivo in pts with ICI-naïve mUM (NCT06581406; RP2-202). **Methods:** This is a randomized, controlled, phase 2/3 study. Key eligibility criteria include age ≥18 years and confirmed unresectable mUM with lesions amenable to injection. Pts with metastatic disease who have had prior exposure to ICIs since the time of UM diagnosis, involvement of >33.3% of the liver, or a history of prior liver- or lesion-directed therapy are not eligible for enrollment. Enrolled pts (N = ~280) will be randomized 1:1 to receive either RP2 + nivo or ipi + nivo. In the RP2 + nivo arm, RP2 will be given intratumorally initially at 1×10^6 PFU/mL, then every 2 weeks (Q2W) at 1×10^7 PFU/mL for 7 doses in combination with intravenous (IV) nivo (240 mg). In the ipi + nivo arm, pts will receive IV ipi (3 mg/kg) and IV nivo (1 mg/kg) Q3W for 4 doses. Pts in both arms may then receive IV nivo at 240 mg Q2W or 480 mg Q4W for up to 2 years from the first dose. The co-primary endpoints are OS and progression-free survival by independent central review using RECIST 1.1. Secondary endpoints are overall response rate, duration of response, disease control rate, clinical benefit rate, duration of clinical benefit, and safety, including incidence of treatment-emergent adverse events (AEs), serious AEs, and immune-mediated AEs. Clinical trial information: NCT06581406. Research Sponsor: Replimune, Inc.

TPS9598 Poster Session

The MATRiX trial: A multicenter, randomized, phase II study of ATR inhibition (via tuvusertib) with or without avelumab in patients with advanced anti-PD-(L)1–refractory Merkel cell carcinoma.

Rashmi Bhakuni, Evan Thomas Hall, George Ansstas, Shailender Bhatia, Andrew Scott Brohl, Melissa Amber Burgess, Maya Dimitrova, Ling Gao, Jeffrey Joseph Ishizuka, Evan J. Lipson, Jose Lutzky, Ann W. Silk, Jina Yun, Isaac Brownell, Judy Murray, Yvonne Marie Mowery, Ted Gooley, Steven Gore, Suzanne Louise Topalian, Paul Nghiem; University of Washington Medicine Dermatology, Seattle, WA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; Division of Medical Oncology, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; UPMC Hillman Cancer Center, Pittsburgh, PA; NYU Langone Medical Center, New York, NY; UCI School of Medicine, Irvine, CA; Yale School of Medicine, New Haven, CT; Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Fred Hutchinson Cancer Center, Seattle, WA; United States National Institutes of Health, Bethesda, MD; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; UPMC Hillman Cancer Center, Department of Radiation Oncology, Pittsburgh, PA; Fred Hutchinson Cancer Research Center, Seattle, WA; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD

Background: Merkel cell carcinoma (MCC) is a rare neuroendocrine skin cancer driven by UV mutations or the Merkel cell polyomavirus (MCPyV).It is aggressive, with a high Ki-67 proliferative index.Despite an initial high response rate (~55%) to PD-1 pathway inhibitors, >50% of patients exhibit primary or acquired resistance.ATR (ataxia telangiectasia and Rad3-related) kinase, a critical cell cycle checkpoint regulator, ensures genome fidelity in cancer cells experiencing high replication stress, including MCC.Our preclinical findings suggest anticancer activity of ATR inhibition via transcriptional induction of NF-κB-associated proinflammatory mechanisms.The potent, selective, orally administered ATR inhibitor tuvusertib (M1774) has shown antitumor activity in patients with unresectable solid cancers in Phase I trials, with a recommended Phase II dose of 180 mg daily on an intermittent schedule.We hypothesize that tuvusertib ± anti-PD-(L)1,may induce tumor regression in advanced anti-PD-(L)1-refractory MCC. **Methods:** The multicenter, randomized Phase II MATRiX trial tests the safety and efficacy of tuvusertib monotherapy (Arm 1) and tuvusertib plus avelumab (Arm 2) in patients with metastatic MCC refractory to PD-(L)1 blockade. Patients with progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 within 120 days of their last anti-PD-(L)1 therapy are eligible. Subjects randomized to Arm 1 receive tuvusertib 180 mg QD on days 1-14 of each 21-day cycle. Subjects in Arm 2 also receive avelumab 1600 mg IV on day 1 of each 21-day cycle. Imaging studies performed 9 weeks after treatment initiation and every 12 weeks thereafter will be assessed per RECIST v1.1. Patients in Arm 1 with progressive disease may receive tuvusertib + avelumab. Treatment-emergent adverse events are graded per Common Terminology Criteria for Adverse Events version 5.0. The primary endpoint is progression-free survival (PFS). Between June 2024 and January 2025, 13 subjects were enrolled across 10 centers. With a targeted enrollment of 50 patients, this trial has 83% power to observe a statistically significant (one-sided level of 10%) difference in PFS if the true hazard ratio for failure is 2.0. A stratified (primary vs. acquired resistance) log-rank test will be used, and binary outcomes will be compared using a Mantel-Haenzel test. A Wieand-like futility rule will be used for an interim analysis after the 23rd event occurs. Tumor biopsies, blood, and stool specimens will be profiled to gain integrated insight into transcriptomic, proteomic, and metabolic signatures associated with immune-mediated therapeutic outcomes. This orthogonal approach to solid tumor immunotherapy, relevant to analogous cancers, will guide future combination strategies to better harness the anti-tumor immune response. Clinical trial information: NCT05947500. Research Sponsor: NCI Cancer Therapy Evaluation Program-Experimental Therapeutics Clinical Trials Network; P30CA015704.

TPS9599 Poster Session

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

Jason J. Luke, Ardy Davarifar, Yana G. Najjar, Omid Hamid, Dirk Schadendorf, Michael K.K. Wong, Nikhil I. Khushalani, Paolo Antonio Ascierto, Tawnya Lynn Bowles, Mark Navarro, Giuseppe Gullo, Caroline Robert; UPMC Hillman Cancer Center and University of Pittsburgh, Pittsburgh, PA; University of Tennessee Medical Center, Knoxville, TN; UPMC Hillman Cancer Center, Pittsburgh, PA; The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA; West German Cancer Center, University Hospital Essen, Essen, Germany; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Moffitt Cancer Center, Tampa, FL; Melanoma and Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; Intermountain Medical Center, Murray, UT; Replimune, Inc., Woburn, MA; Gustave Roussy and Paris-Saclay University, Villejuif, France

Background: Melanoma is the fifth most common cancer, with ~100,000 new cases and ~8000 related deaths estimated in the US for 2024. First-line systemic treatment with immune checkpoint inhibitors improves the objective response rate (ORR) and extends progression-free survival (PFS) and overall survival (OS) for patients with advanced disease. Among available treatments, combination anti–PD-1 (nivolumab) + anti–CTLA-4 (ipilimumab) therapy is associated with the highest ORR and best PFS and OS. However, only ~50% of patients respond to treatment, and limited options exist for patients whose melanoma progresses following anti–PD-1–based therapy. Vusolimogene oderparepvec (VO; also known as RP1) is a selectively replication-competent herpes simplex virus type 1–based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R–). Data from a registration-intended cohort of the IGNYTE study (NCT03767348) showed that intratumoral VO + intravenous nivolumab was well tolerated and demonstrated durable, clinically meaningful antitumor activity (ORR, 32.9% per independent central review using Response Evaluation Criteria in Solid Tumors 1.1) in patients with advanced melanoma and confirmed progression on prior anti–PD-1 therapy. IGNYTE-3 will evaluate the OS and clinical benefit of VO + nivolumab for patients with advanced cutaneous melanoma whose disease has progressed after anti–PD-1 and anti–CTLA-4 therapy (or who are ineligible for anti–CTLA-4 therapy) vs physician's choice. **Methods:** IGNYTE-3 (NCT06264180) is a global, randomized, controlled, multicenter, phase 3 trial (currently recruiting). Key eligibility criteria include age ≥12 years; stage IIIb–IV/M1a–M1d cutaneous melanoma; disease progression on ≥8 weeks of an anti–PD-1 and anti–CTLA-4 treatment (administered in combination or in sequence, with anti–PD-1 last); ≥1 measurable and injectable tumor (≥1 cm); and adequate hematologic, hepatic, and renal function. Patients who are not candidates for anti–CTLA-4 therapy may enroll following progression on anti–PD-1 therapy alone. Patients with BRAF V600-mutant melanoma must have received anti-BRAF ± anti-MEK targeted therapy prior to enrollment. Patients (N = ~400) will receive VO + nivolumab or physician's choice (nivolumab + relatlimab, anti–PD-1 monotherapy rechallenge [nivolumab or pembrolizumab], or single-agent chemotherapy [dacarbazine, temozolomide, or paclitaxel/albumin-bound paclitaxel]). The primary endpoint of the study is OS; the key secondary endpoints are PFS and ORR per RECIST 1.1. Clinical trial information: NCT06264180. Research Sponsor: Replimune, Inc.

TPS9600 **Poster Session**

A phase 1, open-label, dose expansion cohort of the tolerability of tolododekin alfa (ANK-101) in combination with cemiplimab in cutaneous squamous cell carcinoma.

Jong Chul Park, Marcus O. Butler, Brendan D. Curti, Gail Iodice, Danielle M. Pastor, Joseph Elassal, Howard L. Kaufman, John M. Kirkwood; Massachusetts General Hospital, Boston, MA; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Earle A Chiles Research Institute, Portland, OR; Ankyra Therapeutics, Cambridge, MA; National Cancer Institute, National Institutes of Health, Bethesda, MD; UPMC Hillman Cancer Center, Pittsburgh, PA

Background: IL-12 stimulates innate and adaptive tumor immunity. Tolododekin alfa (ANK-101) is an anchored drug conjugate that creates a strong link between full-length IL-12 and aluminum hydroxide through an alum-binding protein (ABP) which localizes IL-12 to the tumor microenvironment (TME), resulting in sustained drug release, prolonged antitumor immune activation, increased PD-L1 expression, and minimal systemic adverse events. Cemiplimab is an anti-PD-1 monoclonal antibody approved in several countries worldwide for the treatment of metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or radiation. This phase 1 clinical trial is designed to combine tolododekin alfa and cemiplimab to determine tolerability and initial biologic and clinical activity. **Methods:** This is an open-label study to evaluate locally administered tolododekin alfa and cemiplimab in patients with advanced CSCC who progressed on, are refractory to, or intolerant of prior SOC treatment. The combination cohort will consist of 15 participants. Participants will be treated with tolododekin alfa in combination with cemiplimab. Treatment will consist of up to eight cycles of tolododekin alfa in combination with cemiplimab followed by cemiplimab alone for up to one year. Follow-up imaging assessments will be performed every 12 weeks. Eligible participants must have histologically confirmed high-risk locally advanced or metastatic CSCC not amenable to surgical management, accessible tumors for injection and biopsy, and measurable disease by RECIST v1.1. Key exclusion criteria include tumors close to vital structures, uncontrolled bleeding disorders, and prior $\geq$ Grade 3 immune-mediated adverse events (imAEs) following treatment with an agent that blocks the PD-1/ PD-L1 pathway. Primary objectives include safety and tolerability of tolododekin alfa and cemiplimab. Secondary objectives include immunogenicity (ADA), and preliminary clinical activity measured by ORR, DCR, DOR, and PFS by RECIST v1.1. Exploratory objectives include QOL using FACT-G and immune pharmacodynamic (PD) changes. This clinical trial is in progress. Clinical trial information: NCT06171750. Research Sponsor: Ankyra Therapeutics.

TPS9601 **Poster Session**

The TIME trial: Phase II randomized controlled trial of time-of-day–specified immunotherapy for advanced melanoma.

Zachary Buchwald, David C. Qian, Jeffrey Switchenko, Melinda Lynne Yushak, David H. Lawson, Michael Lowe; Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Emory University, Atlanta, GA; Department of Hematology and Medical Oncology at Emory University School of Medicine, Atlanta, GA; Emory University Winship Cancer Institute, Atlanta, GA; Department of Surgery, Emory University, Atlanta, GA

Background: Ipilimumab + nivolumab is standard of care for advanced melanoma patients based on data from the CheckMate 067 trial. The recent 10-year outcomes results were reported with a melanoma specific survival of 52%. While data are very encouraging, 50% of patients still succumb to their disease by 10-years. Preclinical data suggests that the circadian rhythm may influence the anatomic localization, function and activity of T cells, the target of immunotherapy. More T cells in the tumor or tumor-draining lymph node during initial immunotherapy administration may improve clinical responses and long-term outcomes. To investigate this idea, we performed a retrospective analysis, the MEMOIR study, finding that more evening infusions of immunotherapy were associated with significantly worse progression free and overall survival for metastatic melanoma patients. These findings have now been reproduced in other cancer types, in a large meta-analysis, and in pre-clinical mechanistic studies. In light of these data, we hypothesize that patients receiving morning or midday infusions of immunotherapy will have better outcomes than patients receiving infusions in the evening. **Methods:** The TIME trial is a three-arm phase II study of time-of-day specified administration of standard dose ipilimumab + nivolumab for metastatic melanoma. Newly diagnosed unresectable metastatic melanoma patients will be randomized to receive 4 cycles of ipilimumab + nivolumab every 3 weeks between either 8:00-11:00 (Arm A), 11:00-14:00 (Arm B), or 14:00-17:00 (Arm C). Following these 4 cycles, they will receive standard of care maintenance nivolumab in a time-of-day agnostic fashion. Eligible adult patients must have Stage III-IV unresectable cutaneous, acral or mucosal melanoma, no prior immunotherapy within 1 year, ECOG performance status of 0-1, and only asymptomatic brain metastases less than 2 cm. The primary objective is to determine whether progression free survival for Arm A or Arm B is superior to Arm C. Secondary objectives include assessments of adverse events, melanoma specific survival and overall survival. We also plan to evaluate the immune profiles of blood and tumor, when available, to assess the impact of time-of-day administered ipilimumab + nivolumab on the circulating immune responses and the tumor immune microenvironment. A sample size of 99 patients (33 in each arm) was selected for at least 80% power to detect a HR of 0.50 with a Type 1 error rate of 0.1 (2-sided) for a comparison of A vs. C and B vs. C. Research Sponsor: None.

TPS9602 **Poster Session**

Phase I dose escalation and expansion study of PRAME T-cell receptor (TCR) engineered IL15-transduced cord blood–derived natural killer (NK) cells in patients with recurrent and/or refractory melanoma (PRAMETIME-Mel).

Derrick Law Tao, Reham Abdel-Wahab, Ruitao Lin, May Daher, Bin Liu, Rafet Basar, Elizabeth J. Shpall, Katy Rezvani, Adi Diab; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: For patients with relapsed and/or refractory metastatic melanoma (RRFM), there is a critical need to test novel strategies with improved anti-tumor response and safety profile. Adoptive cell therapy (ACT) has been recognized as a promising avenue for addressing the unmet need for more potent anti-tumor approaches. Allogeneic cord blood (CB)-derived natural killer (NK) cell therapies have emerged as a therapeutic alternative to adoptive T-cell therapies given decreased toxicity and feasibility as an "off-the-shelf" therapy, bypassing the manufacturing time and treatment delays associated with autologous T-cell products. PRAME (PReferentially expressed Antigen in MElanoma), a cancer-testis antigen expressed on approximately 95% of cutaneous melanomas and not expressed outside of immune-privileged sites such as the testis, ovary, placenta, and endometrium, is a promising target for allogeneic NK cells engineered with a T cell receptor (TCR) to selectively target melanoma cells. In contrast to autologous T cell therapies that require exogenous systemic IL-2 as a supportive factor, NK cells engineered to express IL-15 have been observed to have minimal side effects while significantly enhancing the in vivo expansion and persistence of the transduced NK cells. PRAME TCR/IL-15 NK, an engineered TCR NK cell therapy, has demonstrated efficacy against melanoma cell lines in vitro and in vivo and safety against normal human cell lines. Building upon these preclinical findings, we propose this trial to explore the safety and efficacy of PRAME TCR/IL-15 NK cells in patients with RRFM. **Methods:** This phase I, single-center, open-label trial will assess the safety, tolerability, and efficacy of PRAME TCR/IL-15 cells in patients with HLA A*02:01 positive RRFM, with no prospective PRAME testing. The primary endpoints are to determine the safety, tolerability, maximum tolerated dose and recommended phase II dose. The secondary endpoints are to assess response and survival. The study will be comprised of dose escalation (4 dose levels, with a dose level -1 in case of excessive toxicities observed in dose level 1) and dose expansion. A maximum of 39 patients will be enrolled, including 24 patients in the dose escalation cohort and up to 15 patients in the dose expansion cohort. Enrolled patients will receive lymphodepletion chemotherapy (fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2) on days -6 to -3, followed by a single dose of PRAME TCR/IL-15 NK cells on day 0. Longitudinal blood and tissue samples will be collected for correlative immune analysis. Clinical trial information: NCT06660420. Research Sponsor: None.

TPS9603 **Poster Session**

Multicenter, randomized, double-blinded, placebo-controlled trial of IFx-Hu2.0 (IFx) as adjunctive therapy with pembrolizumab (pembro) in checkpoint inhibitor (CPI)-naïve patients with advanced or metastatic Merkel cell carcinoma (MCC).

Andrew Scott Brohl, Melissa Amber Burgess, Gino Kim In, Karam Khaddour, Peter M O'Neill, Sunil A. Reddy, Eric D. Whitman, James A. Bianco; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; UPMC Hillman Cancer Center, Pittsburgh, PA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Dana-Farber Cancer Institute, Boston, MA; TuHURA Biosciences, Inc., Tampa; Stanford University, Stanford, CA; Atlantic Health System, Morristown, NJ; TuHURA Biosciences, Inc., Tampa, FL

Background: CPIs have revolutionized the treatment of a wide variety of cancers. Despite their success, the majority of cancers do not respond primarily due to tumor-intrinsic mechanisms allowing immune evasion, and obviating activation of tumor specific cytotoxic T cells (cTc), which are required for CPIs to work. Activation of tumor-specific cTc is thus the goal for most therapies aiming to overcome primary resistance to CPIs. IFx is an innate immune agonist designed to overcome primary resistance to CPIs. It consists of a plasmid DNA, pAc/emm55, encoding for an immunogenic gram+ bacterial protein streptococcal Emm55, combined with a cationic polymer that facilitates cellular uptake of DNA. Intralesional injection of IFx results in Emm55 expression on the surface of tumor cells. Pathogen-associated molecular patterns on gram+ bacteria are recognized by toll-like receptors (TLRs) on innate immune cells. TLRs with CD14 as a co-receptor binds to these bacterial proteins, activating an innate immune response against the tumor cell and the expressed bacterial protein. This causes non-self tumor neo-antigen presentation to naïve B and T cells, resulting in activation of tumor specific cTc and antibodies. Unlike oncolytic viral approaches which rely on tumor lysis and distribution of tumor neoantigens into the tumor microenvironment, IFx causes phagocytosis of intact tumor cells and may provide more comprehensive and efficient antigen presentation, promoting inter-antigenic epitope spreading. In a Phase 1b trial among 23 patients with MCC or cutaneous squamous cell carcinoma (cSCC) that failed to respond to anti-PD(L)-1 therapy, intralesional IFx was well tolerated at weekly injections x3 dosing regimen. Post-protocol rechallenge with CPI resulted in 7 of 11 (63%) patients with MCC experiencing durable (median 19 mos.) complete or partial responses, despite prior failure of the same class of CPI. Based on these results, a randomized, double-blind, placebo-controlled trial to evaluate the potential for adjunctive IFx and pembro to improve response rates in the first-line treatment of CPI naïve patients with advanced or metastatic MCC is planned. **Methods:** 118 CPI naive adults with MCC will be assigned via 1:1 randomization to IFx (0.1mg) or placebo given weekly x3 concurrent with pembro 200 mg IV q3w for up to 2 years, or progression or toxicity. Responses assessed by blinded independent central review per RECIST v1.1 q12w during the first 24 months and q24w thereafter up to 5 years. Adverse events (AEs) will be assessed per CTCAE v5.0 up to 90 days after final treatment. Primary and key secondary endpoints include objective response rate and progression-free survival respectively. Other secondary endpoints are safety, duration of response, and overall survival. Clinical trial information: Pending as of submission deadline. Research Sponsor: TuHURA Biosciences, Inc.

TPS9604 **Poster Session**

TeLuRide-006: An adaptive phase 2/3 study of EIK1001, a Toll-like receptor 7/8 (TLR7/8) agonist, in combination with pembrolizumab in patients with advanced melanoma.

Jason J. Luke, Stéphane Dalle, Yin Wu, Oliver Edgar Bechter, Daniel Brungs, Anna Maria Di Giacomo, Hanna Eriksson, Peter Mohr, Rossanna C. Pezo, Egle Ramelyte, Bernardo Leon Rapoport, Gareth Rivalland, Amitesh Chandra Roy, Mizuho Fukunaga-Kalabis, Geetha Krishna Kaza, Yayan Zhang, Etah Kurland, Alexander M. Eggermont; UPMC Hillman Cancer Center, Pittsburgh, PA; Dermatology, Hospices Civils de Lyon, Cancer Research Center of Lyon, Pierre-Bénite, France; King's College London, London, United Kingdom; UZ Gasthuisberg - Katholieke University Leuven, Leuven, Belgium; Wollongong Hospital, NSW, Illawarra, Australia; University of Siena, Center for Immuno-Oncology, University Hospital of Siena, NIBIT Foundation Onlus, Siena, Italy; Department of Oncology-Pathology, Karolinska Institute, Theme Cancer. Oncology-Pathology Department, Karolinska University Hospital-Solna, Stockholm, Sweden; Department of Dermatology, Elbe-Kliniken, Buxtehude, Germany; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; The Medical Oncology Centre of Rosebank, Clinical and Translational Research Unit, Department of Immunology, Faculty of Health Sciences, University of Pretoria, Saxonworld, South Africa; Auckland City Hospital, Auckland, New Zealand; Flinders Centre For Innovation in Cancer, Adelaide, Australia; Merck & Co., Inc., Rahway, NJ; Eikon Therapeutics, Inc., New York, NY; Princess Máxima Center, Utrecht, Netherlands

Background: Immune checkpoint inhibitors (ICIs) relieve immunosuppression of tumor-reactive T cells and enhance antitumor response. Significant advances for the treatment of advanced melanoma have been made using ICIs, with overall survival (OS) benefit conferred by ICI monotherapy. While encouraging results have been observed with combinations of ICIs, no α-controlled, statistically significant OS benefit of combinations over monotherapy has been demonstrated in Phase 3 studies. Despite these advances, 5-year survival for advanced disease is only 15 to 20%, motivating development of new therapies. EIK1001 is a TLR7/8 agonist that stimulates myeloid and plasmacytoid dendritic cells, activating immune and inflammatory responses. This dual activity, distinct from effects on checkpoint proteins, enhances antitumor T-cell activity alone or in combination with ICIs. **Methods:** TeLuRide-006 (NCT#06697301) is a global, multicenter, randomized, double-blind, adaptive Phase 2/3 study of EIK1001 or placebo in combination with pembrolizumab (pembro) as first-line therapy in participants (pts) with advanced melanoma. This study includes dose-optimization (DO), in which pts are randomized 1:1:1 to receive 1 of 2 doses of EIK1001 or placebo in combination with pembro, followed by adaptive Phase 2/3 expansion at the Selected Dose of EIK1001 + pembro or placebo + pembro. Interim analyses will determine whether the study advances from DO to Phase 2 to Phase 3. EIK1001 or placebo is administered intravenously QW until the end of Week 27 then Q3W. Pts are stratified by prior anti-PD-1 adjuvant therapy, LDH level, and BRAF mutational status. Key eligibility criteria: pts $\geq$ 18 years of age with a life expectancy of $\geq$ 3 months, Stage 3 (unresectable) or Stage 4 metastatic melanoma, known BRAF V600 mutational status (or consent to BRAF mutation testing), $\geq$ 1 measurable lesion by RECIST v1.1, and no history of or current pneumonitis/interstitial lung disease. Primary objectives are to evaluate the efficacy and safety of 2 doses of EIK1001 in combination with pembro (DO only) and to compare progression-free survival per RECIST 1.1 by blinded independent central review (BICR) and OS of pts receiving EIK1001 + pembro relative to pts receiving placebo + pembro (at Selected Dose). Secondary objectives include evaluation of the safety and tolerability of the Selected Dose of EIK1001 + pembro relative to placebo + pembro, as well as evaluation of objective response rate and duration of response per RECIST 1.1 by BICR. Exploratory objectives include evaluation of time to objective response, evaluation of potential EIK1001 exposure-response relationships, and evaluation of health-related quality of life, health utilities, and melanoma concerns in pts receiving EIK1001 + pembro relative to placebo + pembro. This study opened on 24 December 2024. Clinical trial information: 06697301. Research Sponsor: None.

TPS9605 **Poster Session**

A phase II study of binimetinib plus imatinib in patients with unresectable KIT-mutant melanoma.

Katy K. Tsai, Gregory A. Daniels, Marjan Rajabi, Nicholas Lee, Adil Daud, Iwei Yeh; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; UC San Diego Moores Cancer Center, La Jolla, CA; University of California San Francisco, San Francisco, CA

Background: Patients (pts) with melanoma refractory to immune checkpoint inhibition (ICI) remain in need of rational therapeutic options. Pts with rare melanoma subtypes (acral, mucosal) are in particular need given lower objective response rates (ORR) to ICI, and lower incidence of BRAF V600-mutant disease. 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 one-third responding as shown in previous phase II studies. A significant number of KIT-mutant melanomas have been shown to demonstrate NF1 or SPRED1 loss, with recent preclinical work showing these alterations to be associated with 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 targeted therapy approach. 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 a multicenter, investigator-initiated phase II study of binimetinib in combination with imatinib in pts with KIT-mutant unresectable melanoma who have progressed on or who are ineligible for ICI. Pts will be ≥18 yo with performance status ECOG 0-2, and have unresectable Stage IIIB/C/D or Stage IV melanoma that is 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/unable to tolerate SOC therapies. Pts with brain metastasis will be eligible if clinically stable with no need for CNS-specific treatment 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 Stage 1. If there are <1 responses, the study will be stopped. Otherwise, 10 additional pts will be accrued in Stage 2 for a total of 25. The null hypothesis that the true response rate is 0.1 will be rejected if ≥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 ≥16 weeks), safety profile (CTCAE). Exploratory objectives include investigation of association between clinical response and baseline NF1 and SPRED1 status, and pathologic correlates of acquired resistance. 11 pts have been screened; 8 of planned 15 pts in Stage 1 have been enrolled. Enrollment is ongoing at UCSF and UCSD. Clinical trial information: NCT04598009. Research Sponsor: None.

TPS9606 **Poster Session**

Neoadjuvant cemiplimab in cutaneous basal cell carcinoma of the head and neck.

Eric Mastrolonardo, Hannah Kenny, Alban Linnenbach, Madalina Tuluc, Stacey Gargano, Scott W. Keith, Rita Susan Axelrod, Voichita Bar-Ad, Arielle Thal, Richard A. Goldman, David Cognetti, Adam J. Luginbuhl, Michael Topf, Michael Rabinowitz, Donald Weed, Wenyin Shi, Sara E. Lally, Carol L. Shields, Jennifer Maria Johnson, Joseph M. Curry; Department of Otolaryngology Head & Neck Surgery, Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University Hospital, Philadelphia, PA; Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University, Pathology Department, Philadelphia, PA; Division of Biostatistics, Department of Pharmacology & Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA; Jefferson Kimmel Cancer Center, Philadelphia, PA; Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University Hospital, Department of Otolaryngology - Head and Neck Surgery, Philadelphia, PA; Department of Otolaryngology, Thomas Jefferson University, Philadelphia, PA; Vanderbilt University School of Medicine, Nashville, TN; Oculoplastic and Orbital Surgery Service, Wills Eye Hospital, Philadelphia, PA; University of Miami Health Systems, Department of Otolaryngology, Miami, FL; Ocular Oncology Service, Wills Eye Hospital, Philadelphia, PA; Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA

Background: Surgical resection of locally advanced basal cell carcinoma of the head and neck (laBCCHN) is often not feasible due to tumor size and proximity to vital structures with risk of significant deformity. Prior data suggest that neoadjuvant therapy could have a major impact on preserving critical structures, especially in the head and neck. The PD-1 inhibitor cemiplimab (REGN2810) has shown significant response rates for metastatic BCC after progression or intolerance of Hedgehog inhibitor (HHI) therapy. However, cemiplimab has not been investigated in the neoadjuvant setting for laBCCHN. To address this gap, this multi-center phase II study seeks to assess the response to neoadjuvant cemiplimab in the treatment of HHI-naïve laBCCHN. **Methods:** Patients with HHI-naive laBCCHN will receive response-adaptive, neoadjuvant IV cemiplimab 350mg every 3 weeks for an initial 2 cycles. The primary endpoint is the fraction of patients demonstrating clinical response after 2 cycles. All patients will undergo RECIST v1.1 response assessment by CT or MRI, and if not radiographically measurable, caliper measurement will be utilized to evaluate the primary endpoint. Those with RECIST v1.1 progression or stable disease with >5% growth will be considered non-responders and will proceed with surgery or other standard of care (e.g. HHI). Patients with stable disease (+5% to -20%) and RECIST v1.1 response will be considered responders and will continue to additional cycles of therapy and clinical assessment (imaging every 2 cycles, total cycles = 6). Patients with complete clinical response prior to completing 6 cycles may proceed to surgery for resection or biopsy of tumor site. Secondary endpoints include rate of functional organ preservation, pathologic response, safety, and quality of life. Correlative analyses will be performed on pre- and post-cemiplimab tumor specimens and peripheral blood samples to assess treatment-related changes in the immune microenvironment related to functional changes in immune cell composition. This study is open with 22 patients enrolled at the time of submission, with a planned total enrollment of 35 patients. Clinical trial information: NCT05929664. Research Sponsor: Regeneron Inc.

TPS9607 Poster Session

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

Urvashi Mitbander Joshi, Jabra Zarka, Hong Wang, Yan Zang, Amy Rose, John M. Kirkwood, Jason J. Luke, Hassane M. Zarour, Diwakar Davar, Yana G. Najjar; UPMC Hillman Cancer Center, Pittsburgh, PA; Mayo Clinic, Rochester, MN; University of Pittsburgh, Pittsburgh, PA

Background: The majority of 100,000 annual new U.S. cases of mel consist of localized early-stage disease that undergo wide local excision (WLE) +/- SLN biopsy (SLNB). The tumor draining lymph node is the initial site of immune response including formation of tumor mediated immune suppression and pre-metastatic niches. SLN positivity is a key prognostic factor in early stage mel. Thus, the SLN is a target for local immune intervention to boost the antitumor response. Vusolimogene oderparepvec (RP1) is an intratumorally administered oncolytic immunotherapy with unique potential for neo-adjuvant therapeutic application. RP1 is constructed from a high potency HSV1 strain (RH018A) modified to replicate selectively in tumors (deletion of neurovirulence factors ICP34.5 and ICP47). RP1 encodes GM-CSF and a fusogenic GALV-GP R- protein to maximize oncolytic potency and induce immunogenic cell death. Preclinical and clinical data demonstrate robust antitumor efficacy (including non-injected lesions) of RP1 alone and in combination with checkpoint inhibitors in advanced mel. This trial addresses a crucial gap in understanding the impact of RP1 on SLN dynamics and preventing disease recurrence in high-risk patients (pts). We hypothesize that in pts with high risk, clinically node negative mel (pT3b-T4b), RP1 will reduce rates of SLN positivity as compared to a historic control by favorably reshaping the immune landscape of the primary tumor, SLN, and the peripheral blood. **Methods:** This is an investigator-initiated, single arm phase 1/2 trial (NCT06216938) designed to assess efficacy and safety of neo-adjuvant RP1 in high-risk, clinically node-negative, non-uveal mel. Eligibility criteria: pT3b, T4a, or T4b non-uveal mel with visible residual tumor or positive biopsy margins, ECOG ≤1, and no prior oncolytic virus therapy. Pts receive 3 doses of neo-adjuvant RP1 (10e6 PFU day 1, 10e7 PFU on days 15 and 21), injected at the primary tumor site followed by standard WLE and SLNB within 35 days of dose 1. Biopsy of residual tumor or archival tumor tissue is obtained pre-RP1 and archival tissue from WLE and SLNB is obtained post-RP1. Blood samples are obtained with each RP1 dose and 3 months post-therapy. Pts are followed for 3 years. Primary endpoint: rate of SLN positivity in the overall cohort. Secondary endpoints: treatment related adverse events (per CTCAE), recurrence free survival, and overall survival. Exploratory endpoints: immunophenotype and microenvironment of the primary tumor, SLN and peripheral blood pre- and post-RP1 (via IHC, IF, and flow cytometry). The observed rate of SLN positivity will be compared to the predicted rate (Melanoma Institute of Australia Prediction Tool for SLN metastatic risk) with a one-sided, one-sample proportion test. Kaplan-Meier estimates will be provided for survival endpoints. The trial is active with 13 of 25 pts enrolled in January 2025. Clinical trial information: NCT06216938. Research Sponsor: Replimune.

TPS9608 **Poster Session**

Lymph node excision (LNEx) for patients with stage III melanoma with one clinically positive node: Excision of Lymph Node trial (EXCILYNT).

Craig L. Slingluff Jr., Hong Zhu, Michael Lowe, Giorgos Constantine Karakousis, Lynn Thacher Dengel, Jay Soong-Jin Lee, Edmund Bartlett, Christina Vadala Angeles, Elizabeth Mary Gaughan, Georgia Beasley, Julia Terhune, Jie Deng, Roger Anderson, Terence Z. Wong, Kim Bullock; University of Virginia, Charlottesville, VA; Emory University School of Medicine, Atlanta, GA; University of Pennsylvania, Philadelphia, PA; Duke University, Durham, NC; Memorial Sloan Kettering Cancer Center, New York, NY; University of Michigan, Rogel Cancer Center, Ann Arbor, MI; Department of Surgery, Duke Cancer Center, Duke University, Durham, NC; University of Maryland School of Medicine, Baltimore, MD; University of Pennsylvania School of Nursing, Philadelphia, PA; Department of Radiology, Division of Nuclear Medicine and Radiotheranostics, Duke University School of Medicine, Durham, NC; University of Virginia School of Medicine, Charlottesville, VA

Background: When melanoma metastases are detected clinically in regional lymph nodes (cLNs) without distant metastasis, standard surgical management is therapeutic lymph node dissection (TLND), which can cause lifelong lymphedema, delay return of function, and reduce quality of life (QOL). Among patients with cLN, 40-50% have metastasis confined to just 1 LN. The goal of this trial is to test a limited lymph node excision (LNEx) for patients with 1 cLN. In a multicenter retrospective analysis of 21 patients treated with LNEx rather than TLND, only 1 (4.8%) developed a LN recurrence in the same node basin, prior to distant disease (same node basin-only recurrence: sNBoR) over ~3 years. Also, only 1 (4.8%) developed lymphedema. To provide more precise estimates of sNBoR and lymphedema rates in a prospective study, and to collect data on HRQOL and return to normal activity after surgery, the EXCILyNT trial was initiated in 2024. The primary hypothesis is that LNEx will provide regional control, with sNBoR of ≤5% at 3 years. The secondary hypothesis is that LNEx will induce lymphedema in ≤6% at 3 years. Exploratory objectives are to assess overall morbidity and HRQOL, to identify features of tumors that may most accurately identify patients with only 1 pathologic LN, and to estimate overall DFS, MSS, and overall survival rates. **Methods:** EXCILyNT is a multicenter, phase II clinical trial for patients with 1 cLN, enrolled on either of two cohorts. All are treated surgically with LNEx: those undergoing surgery first (cohort 1) and those treated with neoadjuvant systemic therapy prior to LNEx (cohort 2). Participants on cohort 2 may receive standard of care neoadjuvant therapy or may be concurrently enrolled in a clinical trial of neoadjuvant therapy, as long as that trial does not mandate TLND. Major eligibility criteria: informed consent, age ≥18 years, ECOG PS 0-2, confirmed metastatic melanoma to only 1 cLN in the axilla, groin, or iliac basin; able to undergo LNEx. The following are excluded: prior LND or radiation therapy of the cLN basin; in-transit or satellite metastases within 1 year; distant metastasis; pre-existing lymphedema that precludes assessment of lymphedema; systemic or intratumoral therapy within 3 months of enrollment. Correlative studies include: evaluation of tumor-involved nodes for immune infiltrates, tumor cell proliferation rates, and somatic mutations; serum collection for cell-free tumor DNA; Health-related quality of life (HRQOL) surveys, FACT-M and Work Productivity and Activity (WPAI) Questionnaire: General health (WPAI:GH) V2.0. The target sample size of 60 eligible participants is chosen to estimate the 3-year rate of sNBoR with an upper CI precision of 7.5% (upper CI limit of 12.5%) using a one-sided Clopper-Pearson exact test. Enrollment is planned to include 7 centers. Thus far, 12 of planned 60 patients have been enrolled at the first 2 centers. Clinical trial information: NCT05839912. Research Sponsor: Philanthropy.

TPS9609 **Poster Session**

NEOSENT: Neoadjuvant anti-PD-1 therapy for patients with high-risk clinical stage II melanoma with a scheduled sentinel lymph node biopsy.

Milton Jose De Barros E. Silva, Matheus Lobo, Andre Molina, Ivan Santos Filho, Manoel Coelho, Monique Celeste Tavares, Joao Paulo S. N. Lima, Rafaela Brito De Paula, Clovis Pinto, João Pedreira Duprat Neto; A.C. Camargo Cancer Center, São Paulo, Brazil

Background: High-risk clinical stage II melanoma patients are already indicated for adjuvant anti-PD-1 therapy, regardless of the sentinel lymph node biopsy (SLNB) result, due to the high risk of relapse associated with pathological stages IIB/IIC or IIIC. Additionally, sentinel lymph node biopsy (SLNB) has no therapeutic effect, although studies have highlighted its prognostic value. Recent data also emphasize that delays in initiating adjuvant anti-PD-1 therapy are linked to poorer relapse-free survival rates. This study aims to investigate whether the early initiation of adjuvant anti-PD-1 therapy, or neoadjuvant anti-PD-1 therapy (for cases where sentinel node biopsy is subsequently classified as positive), is associated with improved outcomes. **Methods:** NEOSENT is a prospective cohort study with a historical control (quasi-experimental study). The inclusion criteria for the prospective cohort are as follows: high-risk clinical stage II melanoma (IIB/IIC) after excisional biopsy with negative margins, age over 18 years, absence of significant concomitant diseases, indication for sentinel lymph node biopsy (SLNB), and access to anti-PD1 treatment. Patients will undergo wide excision margins (WEM) and SLNB, scheduled for week 5 after initiating anti-PD1 therapy. A total of 1 year of anti-PD1 treatment is planned, consisting of either pembrolizumab (200 mg IV every 3 weeks for 18 cycles) or nivolumab (480 mg IV every 4 weeks). The protocol was reviewed and approved by the Institutional Review Board (IRB) prior to implementation. The historical cohort (control arm) includes patients with clinical stage IIB/IIC melanoma who were treated at the AC Camargo Cancer Center with WEM and SLNB, followed by at least one cycle of adjuvant anti-PD1 therapy. The primary objective of the study is to reduce the median time to initiation of anti-PD1 therapy by more than 30 days in the NEOSENT arm compared to the historical cohort. Secondary objectives include comparing relapse-free survival rates between the NEOSENT arm and the historical cohort using propensity score matching, as well as describing the pathological findings of SLNB after neoadjuvant anti-PD1 therapy and their correlation with survival outcomes. Research Sponsor: None.

TPS9610 Poster Session

A phase 2 study to determine the clinical and pathological (path) response to neoadjuvant nivolumab (nivo) and relatlimab (rela) in stage II to IV (M0) resectable cutaneous squamous cell carcinoma (Neo-SCC).

Maria Gonzalez, Alexander Christopher Jonathan van Akkooi, Thomas Bennett, Sydney Ch'ng, Kerwin Frank Shannon, Michael Alexander Rtshiladze, Richard A. Scolyer, Robert V. Rawson, Monica Osorio, Rony Kapoor, Edward Hsiao, Helen Rizos, Serigne N. Lo, Alexander M. Menzies, Angela M. Hong, Georgina V. Long, Ines Esteves Domingues Pires da Silva; Melanoma Institute Australia, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, Australia; Melanoma Institute Australia, Royal Prince Alfred Hospital, Chris O'Brien Lifehouse, The University of Sydney, The Mater Hospital Sydney, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Chris O'Brien Lifehouse, Sydney, NSW, Australia; Melanoma Institute Australia, Wollstonecraft, NSW, Australia; Melanoma Institute Australia, The University of Sydney, and Royal Prince Alfred Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, Royal Prince Alfred Hospital, Camperdown, Australia; Melanoma Institute Australia, I-Med Radiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; Royal North Shore Hospital, I-Med Radiology, Sydney, Australia; Macquarie University, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, Sydney, NSW, Australia; Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, Australia; Melanoma Institute Australia, The University of Sydney, Sydney, Australia, Wollstonecraft, Australia

Background: Cutaneous squamous cell carcinoma (cuSCC) is the second most common skin cancer worldwide (Bray et al. 2018). While 90% of cases are cured surgically (Kauvar et al. 2015), approx. 5% spread regionally or distantly, with an OS rate $<$ 20% at 10 years if regional lymph nodes (LN) are involved (Ogata et al. 2019). Immunotherapy trials have shown efficacy in advanced disease. Neoadjuvant therapy (NAT) is a powerful treatment platform to rapidly assess drug activity in resectable cancers. In melanoma, a major path response to immunotherapy ($\leq$10% viable tumor) correlates with low risk of recurrence in resectable stage III disease (Menzies et al. 2021), and improved OS and EFS when anti-PD1 monotherapy or in combination with anti-CTLA-4 is given neoadjuvantly vs. monotherapy adjuvant (adj) treatment (Patel et al. 2023; Blank et al. 2024). In a study of NAT anti-PD1 monotherapy with cemiplimab, in pts with resectable stage III or IV (M0) cuSCC (N = 20), 55% of pts had a path complete response (pCR) (0% viable tumour) (Ferrarotto et al. 2021). In a larger NAT cemiplimab trial (N = 79) 51% pts achieved pCR (Gross et al. 2022). The De-Squamate cuSCC trial, evaluating NAT anti-PD1 monotherapy with pembrolizumab (N = 27), showed a 63% combined rate of pCR and clinical complete response (CCR) resulting in the de-escalation of surgery and post operative radiotherapy (RT) in 48% of pts, and avoidance of post-operative RT in 15% of pts (Ladwa et al. 2024). The Neo-SCC trial will evaluate if combined PD-1 plus lymphocyte-activation 3 (LAG3) checkpoint inhibition achieves high path response, while allowing for response-driven surgical and RT de-escalation in pts with resectable cuSCC. **Methods:** Pts with histologically confirmed, resectable cuSCC AJCC (8th ed, head/neck) or UICC (9th ed, non-head/neck) clinical stage II, III or IV (M0) are eligible (N = 20). All pts undergo resection (RES) at week 6 following NAT with 2 doses of nivo (480 mg, IV) plus rela (160 mg, IV) at week 0 and 4. LN disease pts undergo baseline index-LN marking and RES at week 6, with subsequent total LN RES if there is no pCR in the index-LN. Synchronous primary/in-transit metastases undergo wide excision during index-LN resection. Non-LN disease pts showing CCR at week 6 receive an incisional biopsy of the baseline tumor site. All non-LN pts undergo definitive excision except those with CCR or pCR on biopsy. RT follows standard care. Imaging includes CT and FDG PET/CT at BL, prior to RES, and during the 5-year follow-up period. Tumor, blood and faecal samples are collected at BL, RES, and recurrence. The primary endpoint is the pCR rate at RES. The sample size is powered to detect a difference $>$ 25% in pCR rate with the historical control. Secondary endpoints include surgical/RT de-scalation rates, RFS, OS, safety/tolerability, surgical outcomes, QOL, and biomarker analyses. Clinical trial information: NCT06288191. Research Sponsor: Bristol Myers Squibb (drug only).

TPS9611 **Poster Session**

A phase Ib study to assess the safety and efficacy of autologous tumor infiltrating lymphocytes (lifileucel) with adjuvant pembrolizumab (PEMBRO) for treatment of immunotherapy naïve patients with high-risk clinical stage IIIb-d resectable melanoma (MEL).

James Isaacs, Lucy Boyce Kennedy, Anthony P. Tufaro, Mark D. DeLacure, Anthony Visioni, Eren Berber, Daniel Raymond, Paolo Fabrizio Caimi, John C. Molina, Yee Peng Phoon, Joshua Arbesman, Jennifer S. Ko, Jan Joseph Melenhorst, Joseph J. Skitzki, Craig Steven Sauter, Brian Gastman, Thach-Giao Truong; Cleveland Clinic, Cleveland, OH; Cleveland Clinic Foundation - Taussig Cancer Institute, Cleveland, OH; Iovance Biotherapeutics, Inc., San Carlos, CA

Background: Despite significant advances in the treatment (Tx) of stage III MEL, there remains a high risk of recurrence after surgical resection. Adjuvant immune checkpoint inhibitors (ICI) are a standard of care, but recurrence rates remain greater than 40% at 5 years. Neoadjuvant ICI have shown improved event-free survival compared to adjuvant ICI. However, at time of surgery a significant proportion of patients' (PTS) MEL still do not show a response. Lifileucel is an autologous tumor infiltrating lymphocyte therapy (TIL) that was recently FDA-approved after showing sustained high tumor response rates for pts with ICI-refractory metastatic MEL. For patients with IO naïve stage IV MEL, ORR was 65% for lifileucel + PEMBRO. Offering TIL at earlier stages of MEL may offer several potential benefits to anti-PD-1 alone. In the Tx-naïve setting, T cells are not previously exposed to ICI that can impact the quality of the TIL product. After curative-intent resection, pts will be rendered clinically tumor-free. When TIL are then utilized to address residual microscopic MEL, they will be less impacted by an immunosuppressive tumor microenvironment often accompanying larger disease burden. Earlier stage also limits tumor heterogeneity that can emerge in more advanced Tx-refractory metastatic MEL. Here we share details of a first clinical trial to evaluate lifileucel with adjuvant PEMBRO for resectable clinically detected high-risk MEL. **Methods:** This phase 1B trial is enrolling pts with clinically detectable stage IIIB-D MEL who are planned to undergo surgical resection and eligible for standard adjuvant anti-PD1. Pts' MEL must be considered fully resectable and pts cannot have previously received ICI. Pts proceed to standard of care resection after enrollment at which time tumor is procured for lifileucel/TIL manufacturing. Once the TIL product has completed manufacturing, pts will receive lymphodepleting chemotherapy followed by TIL infusion and IL2, for up to 6 doses. At week 12 after receiving lifileucel, pts start adjuvant PEMBRO to complete 1 year of Tx. The primary endpoints of this trial are disease free survival at 1 year and safety. The trial is planned to enroll 12 pts. Sample size justification is aimed on detecting 20% improvement on 12-month RFS for lifileucel+ PEMBRO compared to standard Tx. Based on Simon's two-stage design with a one-sided type I error of 0.05 and power of 80%, if 7 or fewer of 11 pts remain relapse-free at 12 months, futility is determined. If 8 or more of 11 are still relapse-free at 12 months, then futility is rejected. Correlative studies include analysis of the phenotype, function and TCR repertoire of baseline TIL samples. Serial PBMC will be collected to monitor TIL persistence (based on TCR analysis) and functional activity. Clinical trial information: NCT06190249. Research Sponsor: Iovance.

TPS9612 **Poster Session**

Trial in progress: A phase 3 randomized study of low-dose intralesional cemiplimab versus primary surgery for patients with early-stage cutaneous squamous cell carcinoma (CLEAR CSCC).

Michael Robert Migden, Sherrif Ibrahim, John Strasswimmer, Nathalie Zeitouni, Suk-Young Yoo, Frank A. Seebach, Israel Lowy, Mihaela C. Cristea, Matthew G. Fury; The University of Texas MD Anderson Cancer Center, Houston, TX; Rochester Dermatologic Surgery, P.C., Victor, NY; Dermatology Associates of the Palm Beaches, Delray Beach, FL; Medical Dermatology Specialists, Phoenix, AZ; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Cemiplimab 350 mg administered intravenously every 3 weeks is approved for the treatment of advanced cutaneous squamous cell carcinoma (CSCC). Surgery is the standard of care for early-stage CSCC; however, for patients who prefer non-surgical management of early-stage CSCC, low-dose intralesional (IL) cemiplimab has demonstrated promising clinical activity in a pilot study (NCT03889912). The purpose of this study (NCT06585410) was to determine the non-inferiority of IL cemiplimab versus primary surgery, along with its safety, tolerability, and efficacy in patients with early-stage CSCC. **Methods:** In this phase 3, randomized, open-label, multicenter study, approximately 369 patients with early-stage CSCC will be randomized 2:1 to cemiplimab (5 mg IL every week for 6 weeks) versus primary surgery. Key inclusion criteria include: patients aged ≥18 years; a histologically confirmed invasive CSCC target lesion that is ≥1.0–≤2.0 cm (longest diameter) located in the head and neck, hand, or pre-tibial surface; adequate performance status; and adequate hepatic, renal, and bone marrow function. Key exclusion criteria include target lesion of keratoacanthoma, autoimmune disease requiring treatment with systemic autoimmune suppressants, concurrent or prior solid tumor or hematologic malignancy (except for protocol-allowed exceptions), and a history of solid organ transplant. Patients will be followed for approximately 3 years. The primary objective is to assess the non-inferiority of IL cemiplimab versus primary surgery by event-free survival. Secondary objectives include safety, tolerability, longest diameter of surgical defect after resection in both arms, and composite complete response in the experimental arm. Study recruitment is planned to start in 2025. Enrollment is planned at study sites across North America, Australia, and Europe. Clinical trial information: NCT06585410. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS9613 **Poster Session**

A phase II randomised study to evaluate the antitumour activity of roginolisib, a novel non-ATP competitive and allosteric modulator inhibiting PI3Kδ, in patients with metastatic uveal melanoma (OCULE-01).

Paul D. Nathan, Anna Maria Di Giacomo, Josep M. Piulats, Giusy Di Conza, Tracey Hammett, Paramjit Kaur, Karen Tonge, Lars Anders van der Veen, Michael M. F. Lahn; Mount Vernon Hospital, Northwood, United Kingdom; University of Siena, Center for Immuno-Oncology, University Hospital of Siena, NIBIT Foundation Onlus, Siena, Italy; Fundacio Institut D'Investigacio Biomedica de Bellvitge, L'Hospitalet del Llobregat, Barcelona, Spain; iOnctura, Geneva, Switzerland; iOnctura SA, Geneva, Switzerland; iOnctura SA, Genève, Switzerland

Background: Uveal melanoma (UM) is a rare malignancy that develops from melanocytes in the eye. At least half of the patients develop metastases, primarily in the liver, and survival outcome from the time of metastatic disease is poor. Patients with second or third line systemic therapy may have a median Overall Survival (OS) ranging from 7 to 12 months. The small molecule roginolisib (IOA-244) is a novel highly selective, non-ATP competitive, allosteric modulator targeting phosphoinositide 3-kinase delta (PI3Kδ). The clinical development of roginolisib investigates its role in PI3Kδ-dependent malignancies. PI3Kδ in solid tumours, including cutaneous and uveal melanoma. Based on previous non-clinical studies, PI3Kδ appears to be up-regulated in tumour cells through inflammation and cellular transformation. In addition to this tumour-cell intrinsic mechanism, roginolisib is designed to block tumour-cell extrinsic mechanisms, including T regulatory (Treg) cells, B cells, and, to a lesser extent, myeloid-derived immune cells. **Methods:** The study OCULE-01 is a Phase II open-label, randomised, parallel-arm, multi-centre study, which will assess the clinical efficacy of oral roginolisib as monotherapy against a control consisting of Investigator´s treatment in patients with metastatic UM who have progressed on prior first line treatment. Eighty-five patients will be enrolled across 20 sites in the EU, UK, and US. Patients will have progressed following at least 1 prior immunotherapy treatment. Patients will be randomised to one of 3 treatment arms; Arm 1: (n=50) IOA-244 80mg daily, Arm 2: (n=25) Investigator's choice of therapy, Arm 3: (n-10) IOA-244 40 mg daily. The primary objective is to assess the overall survival of roginolisib versus Investigators' choice of therapy. Secondary endpoints include PFS, OR, Safety, and Quality of Life impact. Correlative aims include assessing blood and tissue biomarkers (i.e. Treg, ctDNA, gene expression, proteomics etc.) for association with clinical benefit and radiomic analysis of imaging. A final analysis will be performed to assess efficacy after 72 patients become evaluable. Study Centres are currently being opened for enrolment. Clinical trial information: NCT06717126. Research Sponsor: iOnctura.