Effects of immune-enhancing nutrition on radical cystectomy outcomes: Primary results from the randomized phase III double-blind clinical trial (S1600).

Jill Hamilton-Reeves, Joseph M. Unger, Jeffrey Holzbeierlein, Danika Lew, James Ryan Mark, Siamak Daneshmand, Janet Baack Kukreja, Eugene K. Lee, William Tabayoyong, Dawn L. Hershman, Michael Jordan Fisch, Norah Lynn Henry; University of Kansas Medical Center, Kansas City, KS; SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA; Southwest Oncology Group Statistical Center, Seattle, WA; Department of Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA; University of Colorado Denver Department of Radiation Oncology, Aurora, CO; University of Kansas Medical Center, Department of Urology, Kansas City, KS; University of Rochester, Pittsford, NY; Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY; The University of Texas MD Anderson Cancer Center; Carelon Medical Benefits Management, Houston, TX; University of Michigan Rogel Cancer Center, Ann Arbor, MI

Background: SWOG S1600 was a randomized, double-blind, phase III trial comparing the impact of consuming Specialized IMmunonutrition (SIM) to oral nutritional support (ONS) on postoperative complications following radical cystectomy (RC). SIM is fortified with nutrients: L-arginine; omega-3 fatty acids; and dietary nucleotides. **Methods:** Patients with bladder carcinoma planning to undergo RC were enrolled and randomized 1:1 to SIM vs. ONS. The primary endpoint was any (≥Grade I) postoperative complication assessed by the Clavien-Dindo (CD) scale at Day 30 after RC. Multivariable logistic regression was used, adjusted for the stratification factors: diversion type (neobladder vs. ileal conduit), prior neoadjuvant chemotherapy (any vs. none), and baseline nutrition status (well-nourished vs. moderate malnutrition). Additional outcomes included 90-day complications and high-grade (CD ≥Grade III) complications. Two-year progression-free survival (PFS) and overall survival (OS) were assessed; differences by arm were reported using Log-rank test statistics. Protocol-specified intention-to-treat (ITT) analyses based on all randomized patients and 1-sided alpha=.05 tests were performed. **Results:** Among N=203 enrolled patients (99 on SIM, 104 on ONS), median age was 68.8 years, 20% were female and 5% were Black. Five patients did not meet eligibility criteria (1 on SIM, 4 on ONS) but were included under the ITT design. Seventeen patients withdrew consent prior to their Day 30 assessment, and 8 patients were not assessed; thus, n=178 (90 on SIM, 88 on ONS) were evaluable at Day 30. The proportion of patients experiencing CD Grade ≥1 complications was 62.2% for SIM and 58.0% for ONS; in multivariable regression, there was no difference in Grade ≥1 complications by arm (OR=1.18, 95% CI, 0.64-2.18, 1-sided p=.71). There were no differences by arm in high-grade complications at Day 30, in any or high-grade complications at Day 90 or overall. To date, among all 203 patients, 17 on SIM and 26 on ONS have progressed or died, with 2-year PFS estimates of 77.2% and 68.3%, respectively (1-sided p=.16). Nine patients on SIM and 17 on ONS have died, with 2-year OS estimates of 87.4% and 78.2%, respectively (1-sided p=.07). **Conclusions:** There was no difference in any grade CD complications by type of nutritional supplement for patients with bladder cancer undergoing RC. Fewer patients on the SIM arm have progressed or died, although differences were not statistically significant; follow-up for survival will continue through 3-years after enrollment. Future work to understand the interaction of diet on cancers sensitive to immune modulation is needed. Clinical trial information: NCT03757949. Research Sponsor: National Cancer Institute; R37CA218118; NIH/NCI/DCP; UG1CA189974; Nestlé S.A. for provision of nutritional supplements gratis and distribution costs.

Patient-reported outcomes (PROs) from a randomized, phase 3 trial of enfortumab vedotin plus pembrolizumab (EV+P) versus platinum-based chemotherapy (PBC) in previously untreated locally advanced or metastatic urothelial cancer (la/mUC).

Shilpa Gupta, Yohan Loriot, Michiel Simon Van Der Heijden, Jens Bedke, Begoña Pérez Valderrama, Eiji Kikuchi, Aude Flechon, Daniel P. Petrylak, Maria De Santis, Matt D. Galsky, Jae-Lyun Lee, Umang Swami, Srikala S. Sridhar, Ugo De Giorgi, Phoebe Wright, Yi-Tsung Lu, Xuesong Guan, Ryan Dillon, Blanca Homet Moreno, Thomas Powles; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Université Paris-Sud, Université Paris-Saclay, Villejuif, France; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Urology and Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; Hospital Universitario Virgen del Rocío, Seville, Spain; St. Marianna University School of Medicine, Kanagawa, Japan; Centre Léon Bérard, Lyon, France; Yale Cancer Center, New Haven, CT; Department of Urology, Charité University Hospital, Berlin, Germany and Department of Urology Medical University of Vienna, Vienna, Austria; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Princess Margaret Cancer Centre, Toronto, ON, Canada; IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; Pfizer Inc., Bothell, WA; Astellas Pharma, Inc., Northbrook, IL; Merck & Co., Inc., Rahway, NJ; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom

Background: EV+P nearly doubled median progression-free survival and overall survival vs PBC in patients (pts) with previously untreated la/mUC in the phase 3 EV-302 trial. PROs are reported here. **Methods:** In EV-302 (NCT04223856) pts were randomized 1:1 to EV+P or PBC (gemcitabine with cisplatin or carboplatin). PRO assessments included the EORTC Quality of Life Questionnaire (EORTC QLQ-C30), and the Brief Pain Inventory Short Form (BPI-SF) completed at baseline, weekly for 12 weeks (wks), then every 3 wks through survival follow-up, inclusive of the time post-progression. Time to pain progression (TTPP) and mean change from baseline in worst pain at wk 26 using the BPI-SF were prespecified analyses statistically tested using a gatekeeping strategy. Mean change from baseline through wk 26 and time to confirmed deterioration (TTCD) of EORTC-QLQ-C30 and BPI-SF domains were prespecified descriptive analyses. TTPP and TTCD were assessed using Kaplan-Meier methods. **Results:** Of 886 pts randomized, 731 (376 received EV+P; 355 PBC) completed baseline PRO questionnaires. Compliance rates differed between arms and remained >70% through wk 29 for EV+P and through only wk 17 for PBC. Median TTPP was 14.2 months (mos) with EV+P and 10.0 mos with PBC (hazard ratio [HR]=0.92; 95% CI=0.72, 1.17; 2-sided p-value=0.48). The least squares (LS) mean reduction in worst pain at wk 26 was numerically greater with EV+P vs PBC (-0.61 vs -0.03, LS mean difference [95% CI]: -0.58 [-1.05, -0.11] [nominal 2-sided p-value=0.015]). Pts with moderate to severe pain at baseline who were treated with EV+P (n=128, 34%) had a meaningful (>2 pt) improvement from baseline in BPI worst pain from wk 3 through 26. In EORTC QLQ-C30 Global Health Status/Quality of Life [GHS/QoL], EV+P demonstrated a transient worsening at wk 3 (-6.3) that returned to baseline from wks 4 through 26, while patients treated with PBC demonstrated deterioration from wk 1 through wk 17 (range -1.2 to -7.1) when scores returned to baseline. TTCD for EORTC QLQ-C30 GHS/QoL was 5.9 mos with EV+P vs 3.2 mos with PBC (HR = 0.98 [95% CI]: 0.79 – 1.2). **Conclusions:** Pts treated with EV+P have improved survival compared with PBC without detriment to quality of life and functioning, further supporting the value of EV+P for pts with la/mUC. Compliance, especially after progression, was lower than expected (particularly in the PBC arm) and may have impacted the results. Clinical trial information: NCT04223856. Research Sponsor: Seagen Inc. which was acquired by Pfizer in December 2023; Astellas Pharma US; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

Impact of exposure on outcomes with enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer.

Daniel P. Petrylak, Yen Lin Chia, Evan Y. Yu, Thomas Powles, Thomas W. Flaig, Yohann Loriot, Peter H. O'Donnell, Elisabeth I. Heath, Takahiro Kojima, Se Hoon Park, Guru P. Sonpavde, Joel Picus, Nobuaki Matsubara, Wataru Obara, Vaishali Chudasama, Srinivasu Poondru, Michael Harrison, Eric Kim, Sam Joseph Brancato, Jonathan E. Rosenberg; Yale School of Medicine, New Haven, CT; Pfizer Inc., Bothell, WA; Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; University of Colorado Anschutz Medical Campus, Aurora, CO; Université Paris-Sud, Université Paris-Saclay, Gustave Roussy, Villejuif, France; University of Chicago, Chicago, IL; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Department of Urology, Aichi Cancer Center, Nagoya, Japan; Samsung Medical Center, Seoul, South Korea; AdventHealth Cancer Institute, Orlando, FL; Washington University in St. Louis, St. Louis, MO; National Cancer Center Hospital East, Chiba, Japan; Department of Urology, Iwate Medical University, Iwate, Japan; Astellas Pharma US Inc, Northbrook, IL; Astellas Pharma US Inc., Northbrook, IL; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: Enfortumab vedotin (EV) is approved in combination with pembrolizumab and as a monotherapy for locally advanced or metastatic urothelial cancer (la/mUC). EV, alone and in combination with pembrolizumab, has demonstrated an OS benefit and a generally manageable safety profile in patients (pts) with previously treated or untreated la/mUC. Dose modifications, including reductions and interruptions, are recommended to manage EV-related AEs. This analysis evaluates the association between EV plasma exposure, which is impacted by dose modifications, and safety and efficacy outcomes. **Methods:** Characterization of dose- and exposure-response for efficacy and exposure-response for safety outcomes included pts in EV-101 (EV monotherapy 0.75, 1.0, and 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle [3Q4W]), EV-201, and EV-301 (EV monotherapy 1.25 mg/kg 3Q4W). Time-averaged exposure up to an event of interest, C_{avg}, was computed using a population PK model. PK assessment included multiple samples in first 2 cycles, and pre-dose samples in subsequent cycles. **Results:** Dose modifications were common, including dose reductions to 1.0 mg/kg (EV-201 42.1%; EV-301 35.1%) and 0.75 mg/kg (EV-201 13.6%; EV-301 11.1%). EV showed consistent improvement in median PFS and OS vs chemotherapy across all exposure quartiles in EV-301 inclusive of dose modifications (Table). Greater initial EV exposure in the first 2 cycles was associated with a higher ORR and was consistent with dose-response (0.75 mg/kg 21.4% [sample size {n} = 14]; 1.0 mg/kg 18.5% [n = 27]; 1.25 mg/kg 40-51.1% across studies [n = 613]). Lower EV exposure was associated with lower risk of EV-related Grade ≥3 rash or skin reactions, Grade ≥2 peripheral neuropathy, and Grade ≥3 hyperglycemia ($P<0.0001$ for all). **Conclusions:** EV improved PFS and OS outcomes vs chemotherapy in pts with la/mUC across all exposure quartiles. The starting dose of 1.25 mg/kg 3Q4W resulted in EV exposure that maximized likelihood of response. Recommended dose modifications are effective for managing EV-related AEs and should be used as clinically indicated. Clinical trial information: NCT02091999, NCT03219333, and NCT03474107. Research Sponsor: This study was sponsored by Seagen, which was acquired by Pfizer in Dec. 2023.

EV-301	ADC C_{avg} Q1‡ (n = 74)	ADC C_{avg} Q2 (n = 74)	ADC C_{avg} Q3 (n = 74)	ADC C_{avg} Q4 (n = 74)	Chemotherapy§ (n = 307)
Median EV ADI (mg/kg/4 week)† (range)	2.37 (1.15, 3.77)	2.96 (1.57, 3.82)	3.26 (2.36, 3.86)	3.59 (2.50, 3.93)	-
Received any EV dose reduction (%)	54.0	39.2	28.4	20.3	-
To 1.0 mg/kg	52.7	39.2	28.4	20.3	-
To 0.75 mg/kg	21.6	14.9	6.8	1.4	-
Median time to EV dose reduction, months (range)	2.02 (0.79, 9.27)	2.96 (0.95, 12)	3.06 (0.72, 6.64)	2.79 (0.89, 9.04)	-
Median PFS, months (95% CI)	4.44 (3.75, 6.77)	7.16 (5.39, 8.21)	5.62 (5.09, 7.26)	5.65 (5.32, 7.23)	3.71 (3.52, 3.94)
Median OS, months (95% CI)	11.0 (7.89, 15.2)	15.1 (10.8, NE)	15.2 (9.63, NE)	12.6 (9.79, NE)	8.97 (8.05, 10.74)

†Intended ADI was 3.75 mg/kg/4 weeks. ‡Lowest exposure group. §Planned treatment arm. ADI, absolute dose intensity, NE, not evaluable.

4504 Oral Abstract Session

Biomarker analyses in patients with advanced renal cell carcinoma (aRCC) from the phase 3 CLEAR trial.

Robert J. Motzer, Camillo Porta, Masatoshi Eto, Thomas E. Hutson, Sun Young Rha, Jaime R. Merchan, Eric Winquist, Howard Gurney, Viktor Grünwald, Saby George, Julia Markensohn, Joseph E. Burgents, Razvan Cristescu, Yudai Narita, Cixin S. He, Ziming Zhao, Chinyere E Okpara, Yukinori Minoshima, Toni K. CHOUEIRI; Memorial Sloan Kettering Cancer Center, New York, NY; University of Bari "A. Moro" and Policlinico Consorziale, Bari, Italy; Kyushu University, Fukuoka, Japan; Texas Oncology, Dallas, TX; Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Western University, London, ON, Canada; MQ Health, Macquarie University, Sydney, NSW, Australia; University Hospital Essen, Essen, Germany; Roswell Park Cancer Institute, Buffalo, NY; Merck & Co., Inc., Rahway, NJ; Eisai Co., Ltd., Ibaraki, Japan; Eisai Inc., Nutley, NJ; Eisai Ltd., Hatfield, United Kingdom; Dana-Farber Cancer Institute, Boston, MA

Background: In the primary analysis of CLEAR, lenvatinib + pembrolizumab (L+P) significantly improved efficacy vs sunitinib (S) in treatment-naïve patients with aRCC (Motzer 2021). Results were confirmed at the final prespecified OS analysis (Motzer 2024). We report biomarker analyses from CLEAR. **Methods:** PD-L1 IHC 22C3 pharmDx and NGS assays (ImmunoID NeXT platform: WES and RNA-Seq) were performed on archival tumor specimens. To identify somatic alterations including mutations and copy-number variations, paired PBMC samples were used as reference. For RNA-Seq/IHC-derived analyses, a continuous value analysis was performed adjusting by KPS score for: each gene-signature score (T-cell inflamed gene-expression profile [GEP], and non-GEP signatures including proliferation, angiogenesis, hypoxia, MYC, WNT, and other signatures [Cristescu 2022]) vs best overall response (BOR); non-GEP signatures vs BOR adjusted by GEP; and PD-L1 CPS vs BOR. Cutoff analyses were performed for biomarkers that showed significant association in the continuous value analysis. Cutoff values (1st tertile of GEP, or median of non-GEP, signatures) were determined based on combined L+P and S arms. WES analyses were descriptively summarized if TMB/INDEL burden and mutation status of key RCC driver genes were associated with BOR. **Results:** There were no notable differences in baseline characteristics and tumor responses in biomarker analysis sets vs the ITT population. In the L+P arm, the continuous GEP signature score was not associated with BOR. The MYC signature score was negatively associated with BOR (2-sided test, significance criteria 0.1; FDR-adjusted p=0.013/0.012 with/without adjustment by GEP signature score, respectively). The ORRs (95% CI) for the MYC-high and -low groups were 66.3% (56.1-75.6) and 84.0% (75.0-90.8), respectively. In the S arm, the continuous GEP signature score was positively associated with BOR (2-sided test, significance criteria 0.05; p=0.010). The ORRs (95% CI) for the GEP-high and -low groups were 46.9% (38.1-55.9) and 28.8% (18.3-41.3), respectively. The angiogenesis signature was positively associated with BOR (2-sided test, significance criteria 0.1; FDR-adjusted p=0.046/0.088 with/without adjustment by GEP signature score, respectively). The ORRs (95% CI) for the angiogenesis-high and -low groups were 52.1% (41.6-62.5) and 30.4% (21.7-40.3), respectively. PD-L1 CPS and TMB/INDEL burden were not associated with BOR in L+P or S arms. ORR was higher with L+P vs S, regardless of the deleterious mutation status of *BAP1*, *VHL*, *PBRM1*, *SETD2*, and *KDM5C*—frequently mutated genes in RCC. **Conclusions:** The superiority of L+P vs S in ORR does not appear to be impacted by gene-expression signatures for tumor-induced proliferation, angiogenesis, hypoxia, MYC, or WNT, or by PD-L1 status, TMB/INDEL burden or mutation status of RCC driver genes. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Biomarker analysis of the phase 3 KEYNOTE-426 study of pembrolizumab (P) plus axitinib (A) versus sunitinib (S) for advanced renal cell carcinoma (RCC).

Brian I. Rini, Elizabeth R. Plimack, Viktor Stus, Rustem Gafanov, Tom Waddell, Dmitry Nosov, Frederic Pouliot, Boris Alekseev, Denis Soulieres, Sergio Jobim Azevedo, Delphine Borchiellini, Raymond S. McDermott, Rodolfo F. Perini, Julia Markensohn, L. Rhoda Molife, Yiwei Zhang, Michael Nebozhyn, Andrey Loboda, Amir Vajdi, Thomas Powles; Vanderbilt-Ingram Cancer Center, Nashville, TN; Fox Chase Cancer Center, Philadelphia, PA; Dnipro State Medical University, Dnipro, Ukraine; Russian Scientific Center of Roentgenology and Radiology, Moscow, Russian Federation; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Central Clinical Hospital With Outpatient Clinic, Moscow, Russian Federation; CHU of Québec and Laval University, Quebec, QC, Canada; P. A. Herzen Moscow Oncology Research Institute, Ministry of Health of the Russian Federation, Moscow, Russian Federation; Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; Centre Antoine Lacassagne, Université Côte d'Azur, Nice, France; Adelaide and Meath Hospital, University College Dublin, Dublin, Ireland; Merck & Co., Inc., Rahway, NJ; MSD UK, London, United Kingdom; Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute, London, United Kingdom

Background: P + A improved OS, PFS, and ORR over S in 1L advanced RCC in KEYNOTE-426 (NCT02853331).Here, we present exploratory biomarker results including RNAseq, WES, and PD-L1. **Methods:** Patients (pts) with treatment-naive advanced RCC were randomly assigned 1:1 to P + A or S. Association between T-cell–inflamed gene signature ($Tcell_{inf}GEP$), angiogenesis gene signature (RNAseq), and PD-L1 CPS (22C3 IHC) with clinical outcomes were tested at prespecified α=0.05. Other RNA signatures (Cristescu et al. *Clin Cancer Res.* 2022. 2022;28:1680) and molecular subtypes, based on clustering identified from IMmotion151 (Motzer et al. *Cancer Cell.* 2020;38:803), were tested at prespecified α = 0.10 after multiplicity adjustment. DNA mutations (*VHL, PBRM1, SETD2, and BAP1*) by WES were tested at prespecified α = 0.10 after multiplicity adjustment. **Results:** Of 861 pts, 369 (P + A) and 361 (S) had archival samples for RNAseq; 347 (P + A) and 351 (S) had WES samples. PD-L1 CPS was negatively associated with OS (P=0.013) for S. There was a strong positive association of $Tcell_{inf}GEP$ with OS (P=0.003), PFS ($P<0.0001$), and ORR ($P<0.0001$) for P + A. Angiogenesis was positively associated with OS (P=0.013) for P + A; there was a strong positive association with OS ($P<0.0001$), PFS ($P<0.001$), and ORR (P=0.002) for S. For other RNA signatures, positive association with mMDSC was found for PFS (P=0.018) and ORR (P=0.093) with P + A. For S, positive association was found with hypoxia (OS, P=0.034; ORR, P=0.071) and negative associations with MYC (OS, $P<0.001$; PFS, P=0.012) and proliferation (OS, P=0.002). Across all molecular clusters, ORR favored P + A over S, with the highest P + A ORR in the immune/proliferative cluster (Table). By WES, *PBRM1* mutation had positive association with ORR (P=0.004) and PFS (P=0.079) for P + A. For S, positive associations were observed with OS for *VHL* (P=0.073) and *PBRM1* (P=0.001) mutations and a negative one observed for *BAP1* mutation (P=0.046). P + A improved ORR over S regardless of mutational status. **Conclusions:** There was a strong relationship of $Tcell_{inf}GEP$ with clinical outcomes with P + A. Angiogenesis was positively associated with outcomes with S and only with OS with P + A. Further understanding the role of the immune microenvironment in combination therapy will be critical to advance treatment strategies. Clinical trial information: NCT02853331. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Eisai Inc., Nutley, NJ.

	P + A		S	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)
Cluster 1 (angio/stromal)	65	58.5 (45.6-70.6)	69	43.5 (31.6-56.0)
Cluster 2 (angiogenic)	54	64.8 (50.6-77.3)	56	51.8 (38.0-65.3)
Cluster 4 (immune/proliferative)	78	74.4 (63.2-83.6)	80	38.8 (28.1-50.3)
Cluster 5 (proliferative)	56	57.1 (43.2-70.3)	53	34.0 (21.5-48.3)
Cluster 6 (stromal/proliferative)	54	50.0 (36.1-63.9)	55	36.4 (23.8-50.4)
$Tcell_{inf}GEP$ <1st tertile	129	51.9 (43.0-60.8)	114	38.6 (29.6-48.2)
$Tcell_{inf}GEP$ ≥1st tertile	240	65.4 (59.0-71.4)	247	42.1 (35.9-48.5)
110 pts were unable to be assigned into cluster				

Circulating kidney injury molecule-1 (KIM-1) biomarker analysis in IMmotion010: A randomized phase 3 study of adjuvant (adj) atezolizumab (atezo) vs placebo (pbo) in patients (pts) with renal cell carcinoma (RCC) at increased risk of recurrence after resection.

Laurence Albiges, Axel Bex, Cristina Suárez, Robert Uzzo, Xiaobin Tang, Zoe June Assaf, Sarita Dubey, Erik T. Goluboff, Corey Carter, Romain Banchereau, Mahrukh A Huseni, Sumanta Kumar Pal, Brian I. Rini; Gustave Roussy, Université Paris Saclay, Paris, France; Royal Free London NHS Foundation Trust, UCL Division of Surgery and Interventional Science, London, United Kingdom; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Fox Chase Cancer Center, Philadelphia, PA; Genentech Usa, Inc., South San Francisco, CA; Genentech, Inc., South San Francisco, CA; Genentech Inc, South San Francisco, CA; Genentech Inc, San Francisco, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; Division of Hematology Oncology, Vanderbilt University Medical Center, Nashville, TN

Background: In IMmotion010, adj atezo did not prolong investigator-assessed disease-free survival (DFS; primary endpoint) vs pbo after resection in pts with RCC (HR: 0.93, 95% CI: 0.75, 1.15; *P*=0.50; Pal *Lancet* 2023). This exploratory analysis of circulating protein biomarkers was performed to identify high-risk pts with minimal residual disease (MRD) who may show differential benefit from treatment (tx) with atezo. **Methods:** Pts with RCC with clear-cell or sarcomatoid component and increased recurrence risk post nephrectomy were randomized 1:1 to atezo 1200 mg or pbo IV q3w for 16 cycles or 1 year. A retrospective proteomics analysis was done with an affinity-based proximity extension assay (PEA) panel of ≈3000 analytes to identify circulating proteins with differential abundance patterns in matched serum samples (baseline vs at recurrence). A high sensitivity electrochemiluminescence (ECL) assay was then used to evaluate levels of KIM-1, a membrane glycoprotein overexpressed in clear-cell and papillary RCC, in all available baseline and post-tx serum samples. Outcomes in pts with KIM-1 high (≥86 pg/mL) vs low status at baseline were analyzed. **Results:** In pts with matched PEA samples (n=73), circulating KIM-1 was identified as the most significantly enriched protein at recurrence vs baseline. Of 778 pts enrolled in IMmotion010, 752 (97%) had baseline KIM-1 data (high: 300 [40%]; low: 452 [60%]). KIM-1–high status was associated with reduced DFS, and pts with KIM-1 high had better DFS with atezo vs pbo (Table). Longitudinal analysis of matched samples showed that in KIM-1–high pts, 9% (12/138) and 26% (36/141) of pts had a ≥30% increase from baseline in KIM-1 levels at Cycle 4 Day 1 with atezo vs pbo, compared with 16% (34/213) and 12% (25/207) in KIM-1-low pts, respectively. A ≥30% KIM-1 increase was associated with worse DFS in both KIM-1–high (atezo HR: 1.68, 95% CI: 0.77, 3.69; pbo HR: 3.53, 95% CI: 2.24, 5.58) and KIM-1–low (atezo HR: 3.56, 95% CI 2.21, 5.75; pbo HR: 3.22, 95% CI: 1.81, 5.70) subgroups. In pts with matched ECL samples (n=103), median KIM-1 levels were higher (*P*<0.001) at recurrence (172 pg/mL) than at baseline (79 pg/mL). **Conclusions:** In IMmotion010, high baseline serum KIM-1 levels were associated with poorer prognosis but improved clinical outcomes with atezo vs pbo. Increased post-tx KIM-1 was associated with worse DFS. These data suggest that circulating KIM-1 may be a non-invasive marker of MRD and disease recurrence and be associated with benefit from atezo in adj RCC. Further investigation of KIM-1 in adj RCC is warranted. Clinical trial information: NCT03024996. Research Sponsor: F. Hoffmann-La Roche Ltd.

	KIM-1 High		KIM-1 Low	
Median DFS, mo	35.9		57.2	
HR (95% CI)	1.75 (1.40, 2.17)			
	Atezo (n=151)	**Pbo (n=149)**	**Atezo (n=229)**	**Pbo (n=223)**
Median DFS, mo	NE	21.2	57.2	NE
HR (95% CI)	0.72 (0.53, 0.99)		1.12 (0.88, 1.63)	

NE, not evaluable.

Partitioned overall survival: Comprehensive analysis of survival states over 4 years in CheckMate 9ER comparing first-line nivolumab plus cabozantinib versus sunitinib in advanced renal cell carcinoma (aRCC).

Charlene Mantia, Opeyemi Jegede, Hollis Viray, Michael B. Atkins, Lisa Rosenblatt, Xin Yin, David F. McDermott, Meredith M. Regan; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; Bristol Myers Squibb, Princeton, NJ; Dana-Farber Cancer Institute and International Breast Cancer Study Group Statistical Center, Boston, MA

Background: Immunotherapy regimens can be associated with prolonged disease control after treatment discontinuation without the need for further anticancer therapy. An integrated, comprehensive partitioned survival analysis describes how patients spend overall survival (OS) time, on/off treatment, with/without toxicity. Previous analysis of first-line (1L) nivolumab (NIVO) + ipilimumab (IPI) for aRCC in CheckMate 214 showed treatment-free survival (TFS) twice as long vs sunitinib (SUN). TFS and survival states for immune checkpoint inhibitor plus tyrosine kinase inhibitor (TKI) combination are of interest. **Methods:** Overall, 651 patients (pts) with aRCC were randomized to receive 1L NIVO + cabozantinib (CABO) or SUN in the CheckMate 9ER trial; treatment continued until progression or intolerance, NIVO for at most 24 months. Minimum follow-up was 4 years. We partitioned area under the Kaplan–Meier (KM) OS curve into 3 survival states, defined from randomization: time on 1L protocol therapy, TFS, and survival after subsequent systemic therapy (second line [2L]) initiation. TFS and protocol therapy were subdivided as mean times with/without reported grade 2+ treatment-related adverse events (TRAEs). Areas under and between KM curves were estimated by 48-month restricted mean times to event. Bootstrapped 95% CIs for between-group differences are reported. **Results:** At 4 years post randomization, KM estimates of OS were 49.2% vs 40.2% of pts assigned to NIVO+CABO vs SUN, respectively; 17.6% vs 4.7% of pts were surviving treatment-free, and 15.8% vs 8.2% were continuing on 1L protocol therapy. Over the 48-month period since randomization (Table), the mean TFS (95% CI) was 2.4 (0.8–3.9) months longer after treatment with NIVO+CABO than SUN. At least half of TFS was spent with toxicity in both treatment groups, resulting in difference in mean TFS (95% CI) without toxicity of 0.7 (−0.4 to 1.8) month. The NIVO+CABO group spent a mean (95% CI) of 8.5 (6.2–10.8) months more survival time on 1L protocol therapy, whereas the SUN group spent a mean (95% CI) of 6.5 (4.4–8.6) months more survival time after 2L therapy initiation. **Conclusions:** Over the 4-year period since initiation of 1L therapy for aRCC, the longer OS achieved with NIVO+CABO was accompanied by 1.5 times longer mean time surviving treatment-free before 2L therapy compared with SUN, a smaller difference than seen for NIVO + IPI vs SUN. Research Sponsor: Bristol Myers Squibb.

Survival State 48-mo Mean Times, Mo	NIVO+CABO (n = 323)	SUN (n = 328)	Difference (95% CI)
OS	35.1	30.7	–
Time on 1L protocol therapy	22.6	14.1	8.5 (6.2–10.8)
Without toxicity	14.3	7.4	6.8 (4.8–8.8)
With toxicity (grade 2+ TRAE)	8.3	6.7	1.7 (0.1–3.2)
TFS	7.0	4.6	2.4 (0.8–3.9)
Without toxicity	3.0	2.3	0.7 (−0.4 to 1.8)
With toxicity (grade 2+ TRAE)	3.9	2.3	1.6 (0.5–2.8)
Survival after 2L initiation	5.5	12.0	−6.5 (−8.6 to −4.4)

Avelumab + axitinib vs sunitinib in patients (pts) with advanced renal cell carcinoma (aRCC): Final overall survival (OS) analysis from the JAVELIN Renal 101 phase 3 trial.

Robert J. Motzer, Konstantin Penkov, Hirotsugu Uemura, Matthew T Campbell, Christian K. Kollmannsberger, Jae-Lyun Lee, Balaji Venugopal, Alfonsus Van Den Eertwegh, Sylvie Negrier, Howard Gurney, Laurence Albiges, Raanan Berger, John Haanen, Brian I. Rini, James Larkin, Manuela Schmidinger, Robin Sandner, Jing Wang, Alessandra Di Pietro, Toni K. CHOUEIRI; Memorial Sloan Kettering Cancer Center, New York, NY; Private Medical Institution, Euromed service, St Petersburg, Russian Federation; Department of Urology, Kindai University Faculty of Medicine, Osaka, Japan; Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; British Columbia Cancer Agency, Vancouver Centre, Vancouver, BC, Canada; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, United Kingdom; Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; University of Lyon, Lyon, France; Department of Clinical Medicine, Macquarie University, Sydney, NSW, Australia; Institut Gustave Roussy, Villejuif, France; The Chaim Sheba Medical Center, Ramat Gan, Israel; Netherlands Cancer Institute, Amsterdam, Netherlands; Vanderbilt-Ingram Cancer Center, Nashville, TN; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Medical University of Vienna, Vienna, Austria; Pfizer Inc., Collegeville, PA; Pfizer Inc., Cambridge, MA; Pfizer S.R.L., Milan, Italy; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: The JAVELIN Renal 101 (NCT02684006) phase 3 trial compared first-line treatment with avelumab + axitinib vs sunitinib in aRCC. The trial previously met one of its primary objectives by showing significantly longer progression-free survival (PFS) with avelumab + axitinib vs sunitinib in pts with PD-L1+ tumors; longer PFS, higher objective response rate (ORR), and an acceptable safety profile were also observed in the overall population. OS data were immature. Here we report the final analysis. **Methods:** Pts with untreated aRCC (any IMDC risk score) were randomized 1:1 to avelumab + axitinib or sunitinib. OS and PFS (by blinded independent central review) in pts with PD-L1+ tumors (SP263 assay) were independent primary endpoints. OS and PFS in the overall population were key secondary endpoints; response and safety were also analyzed. **Results:** Of 886 pts randomized, 560 (63.2%) had PD-L1+ tumors. At data cutoff (August 31, 2023), median follow-up in the avelumab + axitinib and sunitinib arms was 73.7 and 73.6 months, respectively (≥68 months in all pts). Final efficacy data are shown in the Table. In the avelumab + axitinib and sunitinib arms, grade ≥3 TRAEs occurred in 66.8% vs 61.5%, respectively. Second-line therapy was received by 58.1% vs 69.4%, including a PD-(L)1 inhibitor in 18.8% vs 53.6%, respectively. **Conclusions:** The JAVELIN Renal 101 trial provides the longest follow-up for immune checkpoint inhibitor + tyrosine kinase inhibitor combination treatment from a phase 3 trial reported to date. OS analyses favored avelumab + axitinib vs sunitinib but did not reach statistical significance. PFS was longer with avelumab + axitinib vs sunitinib, and responses were durable in a subset of pts. Final analysis results confirm the long-term efficacy and manageable safety profile of avelumab + axitinib treatment in pts with aRCC. Clinical trial information: NCT02684006. Research Sponsor: Pfizer; the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	PD-L1+ Population		Overall Population	
	Avelumab + Axitinib (n=270)	Sunitinib (n=290)	Avelumab + Axitinib (N=442)	Sunitinib (N=444)
OS				
Median (95% CI), mo	43.2 (36.5-51.7)	36.2 (29.8-44.2)	44.8 (39.7-51.1)	38.9 (31.4-45.2)
66-mo rate (95% CI), %	34.2 (28.4-40.1)	29.9 (24.5-35.5)	35.3 (30.7-39.9)	31.8 (27.3-36.4)
HR for OS (95% CI); 1-sided p value	0.86 (0.701-1.057); p=0.076		0.88 (0.749-1.039); p=0.067	
PFS*				
Median (95% CI), mo	13.9 (11.0-17.8)	8.2 (6.9-9.1)	13.9 (11.1-16.6)	8.5 (8.2-9.7)
66-mo rate (95% CI), %	12.9 (8.9-17.6)	3.1 (1.3-6.1)	11.7 (8.6-15.2)	4.1 (2.2-6.8)
HR for PFS (95% CI); 1-sided p value	0.57 (0.469-0.697); p<0.0001		0.66 (0.566-0.769); p<0.0001	
ORR (95% CI), %*	64.8 (58.8-70.5)	31.4 (26.1-37.1)	59.7 (55.0-64.3)	32.0 (27.7-36.5)
DOR*				
Median (95% CI), mo	19.3 (15.1-22.3)	9.7 (7.0-16.6)	19.4 (16.4-22.3)	14.5 (8.7-16.6)
66-mo rate (95% CI), %	16.8 (11.4-23.0)	4.5 (1.2-11.2)	14.8 (10.6-19.7)	7.1 (3.2-13.2)

DOR, duration of response; HR, hazard ratio *Per investigator assessment (RECIST v1.1).

Characterization of complete responders to nivolumab + gemcitabine-cisplatin vs gemcitabine-cisplatin alone and patients with lymph node–only metastatic urothelial carcinoma from the CheckMate 901 trial.

Matt D. Galsky, Guru P. Sonpavde, Thomas Powles, Melanie Claps, Mauricio Burotto, Michael Schenker, Juan Pablo Sade, Aristotelis Bamias, Philippe Beuzeboc, Jens Bedke, Jan Oldenburg, Yüksel Ürün, Ding-Wei Ye, Begoña Pérez Valderrama, Yoshihiko Tomita, Jeiry Filian, Lily Wang, Daniela Purcea, Michiel Simon Van Der Heijden; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Bradford Hill Clinical Research Center, Santiago, Chile; Centrul de Oncologie Sf. Nectarie, Craiova, Romania; Alexander Fleming Institute, Buenos Aires, Argentina; National and Kapodistrian University of Athens, ATTIKON University Hospital, Athens, Greece; Hopital Foch, Suresne Cedex, France; Eberhard Karls University Tübingen, Tübingen, Germany; Akershus University Hospital, Lørenskog, Norway; Ankara University, Ankara, Turkey; Fudan University Shanghai Cancer Center, Shanghai, China; Hospital Universitario Virgen del Rocío, Seville, Spain; Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Boudry, Switzerland; Netherlands Cancer Institute, Amsterdam, Netherlands

Background: In the CheckMate 901 trial, combination nivolumab (NIVO) + gemcitabine-cisplatin (GC) demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) with compelling objective response rates (ORR; 57.6% with NIVO+GC vs 43.1% with GC alone) and deep, durable complete responses (CR; 21.7% with NIVO+GC vs 11.8% with GC alone) in patients (pts) with previously untreated unresectable or metastatic urothelial carcinoma (mUC). Lymph node (LN)-only metastatic disease is a favorable prognostic factor in pts with mUC and a subset of pts achieve durable disease-free, treatment-free survival with GC +/- surgical consolidation. We conducted a post hoc analysis to characterize the subset of pts with CR, with further analysis of pts with LN-only mUC. **Methods:** In the global, open-label, randomized, phase 3 CheckMate 901 (NCT03036098) trial, cisplatin-eligible pts received NIVO 360 mg + GC every 3 wk for ≤6 cycles followed by NIVO 480 mg every 4 wk until disease progression/unacceptable toxicity or up to a maximum of 2 yrs, or GC every 3 wk for ≤6 cycles. Primary endpoints were OS and PFS by blinded independent central review (BICR). ORR per BICR and safety were exploratory endpoints. These post hoc analyses evaluated treatment outcomes in complete responders and in pts with LN-only disease. **Results:** Of the 608 pts randomized, 102 (16.8%) achieved a CR. Baseline disease characteristics of these pts are shown in the Table. As pts with LN-only mUC were enriched in the CR group, additional analysis of this subgroup was performed. Of all randomized pts, 54 treated with NIVO+GC and 56 treated with GC had LN-only mUC. In these pts, the ORR and CR rate was 81.5% (95% CI 68.6-90.7) and 63.0% versus 64.3% (50.4-76.6%) and 33.9% for NIVO+GC and GC, respectively. Median OS (95% CI) in LN-only pts was 46.3 (24.0-NE) mos with NIVO+GC vs 24.9 (21.4-29.9) with GC (HR, 0.58, 95% CI 0.34-1.00), and median PFS (95% CI) was 30.5 (9.6-NE) mos with NIVO+GC vs 8.8 (7.5-10.9) mos with GC (HR 0.38, 95% CI 0.22-0.66). **Conclusions:** NIVO+GC generated deep responses in CheckMate 901 with a fixed duration of chemotherapy and up to 2 years NIVO. Exploratory characterization of pts with CR identified a group of pts enriched with LN-only disease.In pts with LN-only mUC, NIVO+GC induced durable disease control and clinically meaningful improvements in OS and PFS vs GC alone. These results provide additional support for NIVO plus cisplatin-based chemo as a first-line treatment option for pts with mUC. Clinical trial information: NCT03036098. Research Sponsor: Bristol Myers Squibb.

Baseline disease characteristics for Pts with CR.

	NIVO+GC (N = 66)	GC (N = 36)
PD-L1 status ≥1%, n (%)	28 (42.4)	11 (30.6)
Liver metastasis, n (%)	5 (7.6)	1 (2.8)
LN-only disease, n (%)	34 (51.5)	19 (52.8)

A multicenter phase II study of modified FOLFIRINOX for first-line treatment for advanced urachal cancer (ULTMA; KCSG GU20-03).

Jae-Lyun Lee, Inkeun Park, Shinkyo Yoon, Sang Joon Shin, Seong-Hoon Shin, Kwonoh Park, Jung Hoon Kim, Hyo Jin Lee; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonesi University College of Medicine, Seoul, South Korea; Kosin University Gospel Hospital, Busan, South Korea; Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, South Korea; Division of Hematology/Oncology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan Si, South Korea; Department of Medical Science and Internal Medicine, College of Medicine, Chungnam National University, Daejeon, South Korea

Background: Systemic therapy is used for advanced urachal cancer that is not amenable to surgery. However, due to the low incidence of this disease, prospective clinical trials have not been conducted and there is no established standard of care. 5-FU, oxaliplatin, and irinotecan have synergistic mechanisms of action, do not overlap in major side effects, and all have the potential to be effective in urachal cancer. The ongoing ULTIMA trial (NCT04611724) is evaluating the efficacy and safety of modified FOLFIRINOX in patients with advanced urachal cancer. **Methods:** Patients with recurrent or metastatic urachal cancer with measurable lesions received modified FOLFIRINOX (Oxaliplatin 85 mg/m^2 over 2 hours, Irinotecan 150 mg/m^2 over 1.5 hours, Leucovorin 400 mg/m^2 over 2 hours and 5-FU 2400 mg/m^2 over 46 hours) with prophylactic pegteograstim 6 mg SC on day 3 Q2W till 12 cycles (or until progression or unacceptable toxicities). Response evaluation was done every 6 weeks. The primary endpoint is an ORR. The secondary objectives include PFS, OS and incidence of febrile neutropenia. Simon's minimax two-stage design was employed to test null hypothesis P0=17% and P1=36%, with alpha of 5% and beta of 20%. The primary endpoint was met at the first stage and we decided to report the results. **Results:** From April 2021 to November 2023, 21 patients with advanced urachal cancer were enrolled in 5 cancer centers. A median age was 50 (28-68) and 15 were male. Lung was the most frequent site of metastasis (47.6%) followed by lymph node (38.1%) and peritoneal seeding (33.3%). As of December 2023, 18 patients discontinued treatment. A total of 235 cycles were administered with a median of 12 (6-12) cycles per patient. Two patients achieved CR and 11 patients PR with an ORR of 61.9%; the study met the primary endpoint in the first stage. With a median FU duration of 15.2 months, the median PFS was 9.3 months (95% CI, 6.6~12.0) and estimated median OS was 26.4 months (95% CI, 14.7-38.1). The treatment was tolerable and have no unexpected adverse events. Grade 3 adverse events included neutropenia (4.8%), anemia (9.5%), thrombocytopenia (4.8%) and diarrhea (4.8%). There were neither febrile neutropenia nor grade 4 adverse events. **Conclusions:** The first prospective ULTIMA study showed encouraging ORR and PFS in patients with advanced urachal cancer. The regimen is well tolerated without febrile neutropenia with prophylactic pegteograstim. Further analysis of efficacy will be presented. Clinical trial information: NCT04611724.
Research Sponsor: None.

4511 Rapid Oral Abstract Session

Camrelizumab plus apatinib for previously treated advanced adrenocortical carcinoma: A single-arm, open-label, phase 2 trial.

Zhigong Wei, Yuchun Zhu, Lei Cai, Xingchen Peng; Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; Institute of Hepatopancreatobiliary Surgery, Chongqing General Hospital, Chongqing University, Chongqing, China

Background: Adrenocortical carcinoma (ACC) is a rare, aggressive malignancy with dismal prognosis. Therapeutic options for patients with advanced ACC after failure of standard treatments are limited. The clinical benefit of single-agent immunotherapy as second-line therapy was still unsatisfactory. **Methods:** This was an investigator-initiated, prospective, single-arm, open-label, phase 2 trial and conducted at a single medical center. Patients were eligible for inclusion if they were aged at least 18 years; were pathologically diagnosed as unresectable or metastatic ACC; had failed first-line therapy; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; had at least one measurable lesion; and had adequate organ function. The key exclusion criteria included a history of treatment with immunotherapy, anti-angiogenic small molecule TKIs, or anti-angiogenic monoclonal antibodies; a history of uncontrolled hypertension; and a history of an autoimmune condition requiring systemic therapy. All study participants received camrelizumab 200 mg intravenously on the first day of each 3 week cycle, combined with apatinib 250 mg orally once per day until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was objective response rate (ORR), defined as the proportion of participants with complete response (CR) or partial response (PR) per RECIST (version 1.1). **Results:** A total of 21 patients with advanced ACC received at least one dose of camrelizumab and apatinib. ORR was 52% (95% CI, 30 to 74), and the disease control rate was 95% (95% CI, 84 to 100), superior to PD-1 inhibitor monotherapy and first-line standard therapy. The median PFS was 12.6 months (95% CI, 8.4 to 20.9), and the median OS was 20.9 months (95% CI, 11.0 to 20.9). The most common grade 3 - 4 treatment-related adverse events were alanine aminotransferase elevation (28.6%), aspartate aminotransferase elevation (23.8%) and lymphopenia (23.8%). Our exploratory analysis showed higher peripheral blood CXCR3+CD8+ T cell abundance, lower immunosuppressive CD4+ T cell abundance, and higher overlap of clonotypes between tumor-infiltrating T cells and circulating T cells, likely related to preferable response to camrelizumab plus apatinib therapy. **Conclusions:** In conclusion, the combination of camrelizumab with apatinib showed promising activity and acceptable toxicity in advanced ACC patients who failed previous lines of therapy. Pre-treatment peripheral blood immune cell subsets could be regarded as potential predictors of efficacy. Given the promising clinical activity, the potential of camrelizumab with apatinib as first-line therapy for advanced ACC need further evaluated. Clinical trial information: NCT04318730. Research Sponsor: None.

A multi-institution analysis of outcomes with first-line systemic therapy for 99 patients with metastatic chromophobe renal cell carcinoma.

Sahil D. Doshi, Nazli Dizman, Andrea Knezevic, Amina Touma, Reza Alaghehbandan, Yasser Ged, Moshe Chaim Ornstein, Andrew Warren Hahn, Pavlos Msaouel, Martin H Voss; Memorial Sloan Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Cleveland Clinic, Cleveland, OH; Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Chromophobe renal cell carcinoma (ChRCC) represents ~5-10% of all RCCs. Given its rarity, there is limited clinical trial data to guide systemic therapy for metastatic disease. Phase 2 trials have demonstrated that targeted agents inhibiting vascular endothelial growth factor receptor and mammalian target of rapamycin have similar efficacy in ChRCC compared to conventional RCC. However, immune checkpoint inhibitor (IO) containing regimens appear less efficacious compared to other RCC subtypes. Importantly, these efforts have all enrolled < 30 ChRCC patients, and larger scale studies are needed. **Methods:** We conducted a retrospective study of patients with metastatic ChRCC seen at 3 academic centers. Baseline characteristics and treatment outcomes were obtained from EHR review. Patients were categorized into 4 treatment categories: 1) IO + targeted therapy doublets (e.g., lenvatinib plus pembrolizumab) 2) Pure IO monotherapy and doublets (e.g., ipilimumab plus nivolumab) 3) targeted therapy doublets (e.g., lenvatinib plus everolimus) and 4) targeted monotherapy (e.g., sunitinib). We calculated time to treatment failure (TTF) of first-line systemic therapy and overall survival (OS) by the Kaplan-Meier method. Median time-to-event was reported for each treatment category and categories compared with the log-rank test. **Results:** Ninety-nine patients with metastatic ChRCC treated with first-line systemic therapy were included; 62% were male, 44% had sarcomatoid features, and 33% had IMDC favorable risk. Outcomes with TTF and OS are summarized in the table below. Median TTF and 18-month OS rates were 5 months and 58% for the targeted monotherapy group, 15 months and 80% for the IO/targeted doublet group, 17 months and 65% for the targeted doublet group, and 7 months and 83% for the pure IO group. Treatment with any doublet containing a targeted agent compared to targeted monotherapy yielded a superior median TTF (15 vs 5 months, HR 0.48; 95% CI: 0.29, 0.80; p=0.005) and OS (56 vs 23 months, HR 0.56; 95% CI: 0.30, 1.04; p=0.07). Most treatment (64%) was discontinued due to progression; 25% due to toxicity. 11 patients had ongoing treatment at time of analysis. **Conclusions:** In this observational analysis, patients with targeted doublet regimens had a higher median TTF and OS compared to those receiving monotherapies. We continue to build on this dataset and plan to conduct progression free survival analysis. Research Sponsor: None.

TTF and OS by first-line treatment group.

	N	Follow-up Time for Survivors, Months – Median (range)	Median TTF, Months (95% CI)	OS Events	Median OS, Months (95% CI)	18-Month OS Rate (95% CI)
Targeted Monotherapy	54	44 (2, 156)	5 (3, 7)	42	23 (11, 42)	58% (44, 70)
IO/Targeted Doublet	17	22 (6, 50)	15 (2, 24)	6	56 (17, 56)	80% (49, 93)
Targeted Doublet	14	15 (1, 122)	17 (3, 22)	7	99 (6, NR)	65% (31, 85)
Pure IO	14	17 (4, 96)	7 (2, 27)	3	NR	83% (45, 95)

NR = Not Reached.

4513 Rapid Oral Abstract Session

Preliminary safety, pharmacokinetics and clinical activity of DFF332, an oral HIF2α inhibitor, as monotherapy in a phase 1 dose escalation study in patients with advanced clear cell renal cell carcinoma.

Sumanta Kumar Pal, Nizar M. Tannir, Peter Grell, Xin Gao, Ritesh R Kotecha, Joel Picus, Filippo G. De Braud, Shunji Takahashi, Alvin Wong, Cristina Suárez, Javier A Otero, Nicole Kundamal, Xin Yang, Sherif Sharaby, Mike Roy, Patrizia Barzaghi-Rinaudo, Laurence Albiges; Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic; Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA; Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Division of Oncology, Siteman Cancer Center, Washington University, St. Louis, MO; Department of Oncology and Hematology, IRCCS National Cancer Institute Foundation and Full professor of Medical Oncology, University of Milan, Milan, Italy; Department of Medical Oncology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Biomedical Research, Novartis Pharmaceutical Corporation, East Hanover, NJ; Biomedical Research, Novartis Pharma AG, Basel, Switzerland; Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris Saclay University, Villejuif, France

Background: Targeting HIF2α inhibition has been proven to be an effective therapeutic option in patients (pts) with advanced clear cell renal cell carcinoma (ccRCC). DFF332, a small molecule inhibitor that selectively targets HIF2α transcriptional activity, has shown dose-dependent antitumor efficacy in preclinical models of ccRCC. **Methods:** This is the first in human, Phase I/Ib, open-label, multicenter, study (CDFF332A12101, NCT04895748) of DFF332 in adult pts with advanced ccRCC. The study evaluated the safety, tolerability, antitumor activity, pharmacokinetics (PK) and pharmacodynamics of DFF332. Here we report the preliminary data of the dose escalation of DFF332 monotherapy, administered orally at 50 mg or 100 mg weekly (QW) or at 25 mg, 50 mg, 100 mg or 150 mg once daily (QD) in 28-day treatment cycles. **Results:** Between Nov 30, 2021 to Nov 15, 2023, 40 pts (male, 78%) with a median age of 62.5 (38-79) years received treatment with DFF332. All pts received ≥1 prior line of therapy. At data cutoff, 18 pts were continuing treatment, while the treatment was discontinued in 19 pts (48%) due to progressive disease, and in 3 pts (8%) based on the physician's decision. The median (range) duration of exposure was 12.1 (1.0-75.6) weeks. Overall, 37 pts (93%) reported ≥1 adverse event (AE) regardless of relationship to study drug. Most common AEs were fatigue (33%), anemia (30%), increased blood cholesterol, and constipation (each 15%). Treatment-related AEs (TRAEs) were reported in 24 pts (60%): anemia, increased blood cholesterol, fatigue (each 13%), and hypertriglyceridemia (10%) being the most common TRAEs. Grade 3 TRAEs were increased weight and hypertension (1 pt [2.5%] each). Hypertension was the only treatment-related serious AE reported in 1 pt. No grade 4 TRAEs and dose-limiting toxicities have been observed so far. None of the patients reported hypoxia. At cut-off, 18 pts (45%) had stable disease (SD) and two pts (5%) achieved partial response [PR] accounting to a disease control rate (complete response + PR + SD) of 50%. Preliminary PK results demonstrated fast oral absorption, slow elimination, and dose-proportional exposure. **Conclusions:** During this phase I study, the monotherapy of DFF332 has shown a promising safety profile across all doses and schedules. Additionally, there have been indications of clinical activity and a dose-proportional modulation of erythropoietin. Currently, we are conducting an ongoing analysis of the PK and biomarker data, which will be included in the presentation. Clinical trial information: NCT04895748. Research Sponsor: Novartis Pharmaceuticals Corporation.

Systemic treatments in favorable and very favorable risk metastatic renal cell carcinoma (mRCC): Real world evidence from the International mRCC Database Consortium (IMDC).

Martin Zarba, Evan Ferrier, Connor Wells, Talal El Zarif, Naveen S. Basappa, Hedyeh Ebrahimi, Rana R. McKay, Lori Wood, Benoit Beuselinck, Cristina Suárez, Kosuke Takemura, Aly-Khan A. Lalani, Haoran Li, Lavinia Anne Spain, Arnoud J. Templeton, Thomas Powles, Georg A. Bjarnason, Guillermo de Velasco, Toni K. CHOUEIRI, Daniel Yick Chin Heng; Tom Baker Cancer Centre, University of Calgary, Alberta, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Barts Cancer Institute, London, United Kingdom; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Department of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; City of Hope Comprehensive Cancer Center, Duarte, CA; University of California, San Diego Health, La Jolla, CA; Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada; UZ Leuven, Leuven, Belgium; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; McMaster University, Hamilton, ON, Canada; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Peter MacCallum Cancer Centre, Melbourne, Australia; St. Claraspital, Basel, Switzerland; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; Medical Oncology Department, Hospital Universitario 12 De Octubre, Madrid, Spain; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada

Background: The role of immunotherapy combinations in mRCC with IMDC favorable risk is controversial. A very favorable subgroup of favorable risk patients (primary diagnosis to systemic therapy ≥3yr, Karnofsky Performance Status 90 or 100% and absence of brain, liver, or bone metastasis) has been described by Schmidt A. et al., which require characterization in the immuno-oncology combination era. **Methods:** Using the IMDC, we selected mRCC patients with IMDC favorable risk who started systemic therapy during 2016-2023 and examined the favorable risk group and the subset of very favorable risk patients. First line systemic therapy was divided into 3 groups: Ipilimumab + Nivolumab (IPI/NIVO), combination of anti PD1/PDL1 and VEGF (IO-VEGF) (Pembrolizumab and Axitinib or Lenvatinib, Avelumab and Axitinib, or Nivolumab and Cabozantinib), and Vascular endothelial growth factor (VEGF) inhibitors (Pazopanib or Sunitinib). The primary outcomes were 2-year overall survival (2y OS) in the favorable and very favorable risk population. Secondary outcomes included Response Rate (RR), treatment duration (TD) and time to next treatment (TTNT). We used unadjusted survival rates at 2 years, with Cox regression model with TKI mono as reference. **Results:** 611 favorable risk patients were eligible for analysis, of which 165 (26.9%) had very favorable risk disease. Median age at diagnosis was 62 years, 73.8% were male, 87.1% had clear cell histology, 5% had sarcomatoid features, and 97,2% had a prior nephrectomy. With a median follow up of 33 months, outcomes are summarized in the table. **Conclusions:** No significant difference in survival between different treatment regimens in the favorable risk population was detected yet. In the very favorable risk population, there was a statistically significant decrease in 2 year overall survival with IPI-NIVO (HR 3.19) which, if validated, could underline the necessity of targeting the VEGF pathway in this population. Further prospective trials and longer follow-up are required to confirm these findings. Research Sponsor: None.

Summary of outcomes in favorable and very favorable risk patients.

Treatment Arm	IPI/NIVO	IO-VEGF	VEGF	p value
Favorable Risk				
N	91	167	353	
RR	35%	51.4%	37.9%	**p= 0.006**
2yr OS (95% CI)	86.4% (77.4 - 95.4)	84.1% (77.0 - 91.2)	81.1% (76.5 - 85.6)	p= 0.601
OS HR (95% CI)	0.93 (0.56 - 1.54)	0.81 (0.55-1.21)	Reference	p= 0.315
TD (95% CI)	5.7 m (4.0 - 10.8)	22.4 m (19.1 - 29.5)	12 m (10.2 - 13.3)	**p< .0001**
TTNT (95% CI)	22.3 m (14.3 - 38.1)	32.2 m (22.7 - 42.6)	15.8 m (14.0 - 17.7)	**p< .0001**
Very favorable Risk				
N	20	53	92	
RR	23.5%	58.1%	55%	**p= 0.039**
2yr OS (95% CI)	71.3% (46.6 - 96.0)	87.2% (75.4 - 98.9)	92.1% (85.9 to 98.2)	**p= 0.041**
OS HR (95% CI)	3.19 (1.21 - 8.41)	1.11 (0.41-3.05)	Reference	**p= 0.018**
TD (95% CI)	10.6 m (2.9 - 38.7)	32.1m (20.6 - 55.2)	19.4 m (14.7 - 25.5)	**p= 0.05**
TTNT (95% CI)	27.1 m (7.4 - 39.2)	48.3 m (30.0 - NR)	23.2 m (18.3 - 28.8)	**p= 0.024**

4515 Rapid Oral Abstract Session

Investigation of T cell phenotypes associated with response or resistance to immune checkpoint inhibitors (ICI) through single-cell analysis of renal cell carcinoma (RCC).

Soki Kashima, Zhaochen Ye, Alia Meliki, Miya Hugaboom, Nicholas R. Schindler, Jess Graham, Vivien Moritz, Nourhan El Ahmar, Yasmin Nabil Laimon, John Canniff, Renee Maria Saliby, Gwo-Shu Mary Lee, Marc Machaalani, Maxine Sun, Wenxin Xu, Sabina Signoretti, Bradley Alexander McGregor, Rana R. McKay, Toni K. CHOUEIRI, David A. Braun; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Department of Pathology, Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; University of California, San Diego Health, La Jolla, CA

Background: RCC is notable for a high CD8+ T cell infiltration despite its modest tumor mutational load. However, CD8+ T cell infiltration does not correlate with ICI response, highlighting the need to understand cellular composition and phenotype. We conducted a comprehensive dissection of the tumor microenvironment (TME) using pre- and post-ICI treatment samples to identify specific T-cell populations associated with ICI treatment efficacy in RCC. **Methods:** A total of 70 tumor samples (n = 59 clear cell; n = 11 non-clear cell) from 63 patients with RCC were collected before (n = 48) and/or after (n = 22) systemic therapies (VEGFi, n = 9; mono-ICI, n = 20; ICI + ICI, n = 17; ICI + VEGFi, n = 9; others, n = 15). This cohort contained 12 paired samples on pre and post from 5 patients, and 58 unpaired samples. Responders (R) were defined as complete and partial responses (n = 22), and non-responders (NR) as disease progression (n = 33) according to the best response based on RECIST. We performed single-cell RNA-sequence (scRNA-seq) on all samples and established a transcriptomics atlas in RCC. We utilized established gene expression signatures to interrogate cellular composition and functional states for samples from ICI-treated patients. We used non-negative matrix factorization (NMF) to identify gene programs, offering superior feature preservation and interpretability. **Results:** 443,337 high-quality viable cells were annotated to lymphoid, myeloid, tumor, endothelial, or fibroblast compartments, capturing the RCC TME landscape. Among CD8+ T cells, we observed significant heterogeneity, particularly in exhausted T cells (Tex) expressing *PD-1* and *TIM-3*. Tex in NR showed enrichment for tissue-residency and innate-like genes and gene programs, exemplified by significant upregulation of *ZNF683* ($p = 0.031$) and *ITGAE* ($p = 0.0041$). In contrast, Tex in R exhibited a marked upregulation of heat shock protein genes, such as *HSP1B* ($p < 2.22E-16$) and *DNAJB1* ($p < 2.22E-16$), highlighting a distinct genomic profile. Notably, through NMF analysis, Tex in R showed a significantly higher stress response program and terminal exhaustion program than in NR at baseline and after ICI treatment. Further analysis through gene signature scoring showed an association between Tex in R and enhanced IFN and chemokine activities, stress response, and terminal differentiation post-ICI. **Conclusions:** Our single-cell transcriptomic analysis uncovered the relationship between Tex with active stress responses and ICI efficacy, additional suggesting T cell revival with ICI-exposure. This study identifies the specific Tex characteristics associated with ICI responsiveness, highlighting scRNA-seq as a scientific strategy for deep correlative analysis in large patient cohorts, and emphasizing the need for further investigation into the unique intricacies of the RCC TME. Research Sponsor: None.

Avelumab (A) as neoadjuvant therapy in patients (pts) with muscle-invasive urothelial carcinoma (MIUC): Survival data of AURA trial, Oncodistinct 004.

Jeremy Blanc, Aurélien Carnot, Philippe Barthelemy, Vinciane Casert, Lionel Staudacher, Jan Van den Brande, Brieuc Sautois, Vincent Vanhaudenarde, Emmanuel Seront, Veronique Debien, Lieveke Ameye, Nuria Kotecki, Jean Christophe Fantoni, Thibault Tricard, Thierry Andre Roumeguere, Ahmad Awada, Nieves Martinez Chanza; Institut Jules Bordet, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles, Brussels, Belgium; Centre Oscar Lambret, Lille, France; Medical Oncology, Institut de Cancérologie Strasbourg Europe, Strasbourg, France; Centre Hospitalier Universitaire de Ambrois Paré, Mons, Belgium; Hôpital Paris Saint-Joseph, Paris, France; University Hospital Antwerp, Edegem, Belgium; University Hospital of Liège, CHU Sart-Tilman, Liège, Belgium; CHU UCL Namur, Vezin, Belgium; Institut Roi Albert II, Cliniques universitaires Saint Luc, Université Catholique de Louvain, Brussel, Belgium; Institut Jules Bordet, Anderlecht, Belgium; Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet, Brussels, Belgium; Hôpitaux Universitaires de Strasbourg, Strasbourg, France; Erasme Hospital, Hopital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium

Background: Immunotherapy in the perioperative setting of MIUC appears promising. The AURA trial (NCT03674424) investigated the addition of avelumab to neoadjuvant dose-dense MVAC (ddMVAC) or cisplatin-gemcitabine (CG) respectively, followed by surgery in the cisplatin-eligible cohort. The primary endpoint was previously reported with high pathological complete response (pCR) rates with each cisplatin-based regimen. In the cisplatin-ineligible cohort, pts were randomized to neoadjuvant A alone or in combination with paclitaxel-gemcitabine (PG) followed by surgery. Avelumab monotherapy showed encouraging pCR but the addition of PG did not provide any benefit. Here, we report the survival data from cisplatin-eligible and ineligible cohorts of the AURA trial. **Methods:** In the cisplatin-eligible cohort, 79 pts were randomly assigned to the ddMVAC-A (n=39) or CG-A (n=40) groups. In the cisplatin-ineligible cohort, 58 pts were randomly assigned to the PG-A (n=29) or A (n=29) groups. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method at 12 months and 36 months for the overall cohort and by subgroups. **Results:** Median follow-up was 33 months and 45 deaths were reported. In the cisplatin-eligible cohort, 12-month DFS was 92% (95% CI, 83-96%) and 36-month DFS was 72% (95% CI, 57-83%). For ddMVAC-A group: 97% and 77%, respectively. For CG-A group: 86% and 68%. Overall, 12-month OS was 89% (95% CI, 80-95%) and 36-month OS was 73% (95% CI, 61-83%). For ddMVAC-A: 95% and 87%. For CG-A: 84% and 61%. Among the ypT0N0 pts, no events were registered within 12 months of follow-up showing a DFS rate of 100% for both arms. At 36 months no events were reported for pts treated with ddMVAC-A and two for CG-A showing DFS rates of 100% and 78% respectively. In the cisplatin-ineligible cohort, 12-month DFS was 60% (95% CI, 46-72%) and 12-month OS was 71% (95% CI, 57-81%). For PG-A: 52% and 67%. For A: 68% and 75%. Among the ypT0N0 pts, no DFS events occurred within 12 months. Data for 36-month are not yet mature. Overall, the main cause of death was disease progression (73%). **Conclusions:** The addition of neoadjuvant avelumab to cisplatin-based chemotherapy results in a high DFS and OS at 12 and 36 months respectively, especially in pts with complete response to neoadjuvant treatment. Combination with ddMVAC regimen offers robust activity. Cisplatin-ineligible pts had lower survival outcomes with no benefit of PG addition. Clinical trial information: NCT03674424. Research Sponsor: Aspirant F.R.S.-FNRS (Fonds de la Recherche Scientifique); Merck N.V.-S.A., Overijse, Belgium, an affiliate of Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer.

DFS and OS for each treatment arm.

	ddMVAC - A	CG - A	PG - A	A
12-month DFS	97% (95% CI, 83-100%)	86% (95% CI, 70-94%)	52% (95% CI, 32-69%)	68% (95% CI, 47-82%)
36-month DFS	77% (95% CI, 55-89%)	68% (95% CI, 46-82%)	-	-
12-month OS	95% (95% CI, 81-99%)	84% (95% CI, 67-92%)	67% (95% CI, 46-81%)	75% (95% CI, 55-87%)
36-month OS	87% (95% CI, 68-95%)	61% (95% CI, 40-76%)	-	-

LBA4517 **Rapid Oral Abstract Session**

Perioperative sacituzumab govitecan (SG) alone or in combination with pembrolizumab (Pembro) for patients with muscle-invasive urothelial bladder cancer (MIBC): SURE-01/02 interim results.

Antonio Cigliola, Marco Moschini, Valentina Tateo, Chiara Mercinelli, Damiano Patanè, Emanuele Crupi, Renzo Colombo, Vincenzo Scattoni, Giorgio Brembilla, Maurizio Colecchia, Francesco Montorsi, Andrea Necchi; Medical Oncology Department, IRCCS San Raffaele Hospital, Milan, Italy; Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy; IRCCS San Raffaele Hospital, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy; Urology Unit, IRCCS Ospedale San Raffaele, Milan, Italy; Department of Radiology, IRCCS San Raffaele Hospital, Milan, Italy; Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, Milan, Italy

4518 Rapid Oral Abstract Session

Quantitative circulating tumor DNA (ctDNA) assessment in patients (pts) with advanced urothelial carcinoma (UC) treated with pembrolizumab (pembro) or platinum-based chemotherapy (chemo) from the phase 3 KEYNOTE-361 trial.

Thomas Powles, Wayne Yen-Hwa Chang, Yoshiaki Yamamoto, José Muñoz-Langa, Felipe Reyes, Avivit Peer, Evan Y. Yu, Graham Cohen, Anja Lorch, Abhishek Bavle, Blanca Homet Moreno, Julia Markensohn, Mackenzie Edmondson, Cai Chen, Razvan Cristescu, Carol Elaine Pena, Jared Lunceford, Seyda Gunduz; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Taipei Veterans General Hospital, Taipei, Taiwan; Yamaguchi University Hospital, Yamaguchi, Japan; Hospital Universitario Y Politécnico La Fe, Valencia, Spain; Fundación Arturo López Pérez, Santiago, Chile; Rambam Health Care Campus, Haifa, Israel; Fred Hutchinson Cancer Center and University of Washington, Seattle, WA; Life Groenkloof Hospital, Mary Potter Oncology Centre, Groenkloof, Pretoria, Gauteng, South Africa; Universitätsspital Zürich, Zürich, Switzerland; Merck & Co., Inc., Rahway, NJ; Istinye University Liv Hospital, Istanbul, Turkey

Background: ctDNA is emerging as a potential biomarker of disease in early-stage bladder cancer but is less understood in advanced UC. We present a retrospective analysis of pre-treatment and on-treatment ctDNA data by clinical outcomes with pembro monotherapy versus chemo in pts with advanced UC from the phase 3 KEYNOTE-361 trial (NCT02853305). **Methods:** Pts with previously untreated advanced UC were randomly assigned 1:1:1 to pembro + chemo, pembro alone, or chemo alone. Tumor tissue mutations were evaluated with whole exome sequencing of tumor and matched normal DNA. Plasma ctDNA was evaluated using the Guardant Health (GH) Guardant 360 LDT assay. ctDNA changes from pre-treatment cycle 1(C1) to on-treatment cycle 2 (C2) were quantified by maximum variant allele frequency (maxVAF) of tumor tissue–specific mutations (tumor-informed [TI] approach) or GH molecular response (MR) score. Association between C2/C1 ratios or baseline TI maxVAF and clinical outcomes (ORR, PFS, and OS) were evaluated. Nominal statistical significance of maxVAF was prespecified at 0.05 (hypothesis, negative). **Results:** ctDNA samples from 263 pts (n = 131, chemo; n = 132, pembro) were analyzed. Clinical characteristics and baseline ctDNA levels within arms were similar. Lower C1 maxVAF was associated with improved ORR, PFS, and OS in the pembro arm ($P < 0.01$) and was robust to adjustment for TMB and PD-L1, but not in the chemo arm ($P > 0.05$). Larger C2 reductions in ctDNA levels were observed in the chemo vs pembro arm (median ratio of C2/C1 TI maxVAF, 0.03 vs 0.71, respectively); similar observations were made for MR score. ctDNA reductions were associated with improved ORR, PFS ($P < 0.001$), and OS ($P < 0.01$) for TI maxVAF in the chemo arm; MR score was significantly associated with ORR and PFS ($P < 0.01$). Associations were stronger in the pembro arm ($P < 0.001$) and were robust to adjustment for TMB and PD-L1. ctDNA changes from C1 to C2 did not show independent explanatory value for OS when RECIST v1.1 response status was added as a variable. **Conclusions:** ctDNA levels at baseline appear prognostic for pembro. Reductions in ctDNA during the first treatment cycle were associated with outcome. Distinct patterns of ctDNA response were observed with the different treatments, and stronger associations with long-term clinical outcome were observed with pembro. Association of OS for both pembro and chemo was not retained when adjusting for tumor response. Early ctDNA dynamics did not offer additional benefit in predicting outcome beyond radiographic assessment of tumor size change. Clinical trial information: NCT02853305. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Association of machine learning (ML)–derived histological features with transcriptomic molecular subtypes in advanced renal cell carcinoma (RCC).

Niha Beig, Shima Nofallah, David F. McDermott, Robert J. Motzer, Thomas Powles, Brian I. Rini, Hartmut Koeppen, Romain Banchereau, Miles Markey, Isaac Finberg, Geetika Singh, Limin Yu, Robert Egger, Chintan Parmar, Jake Conway, Stephanie Hennek, Daniel Ruderman, Samuel Vilchez, Mahrukh A Huseni, Jennifer Margaret Giltnane; Genentech, South San Francisco, CA; PathAI, Boston, MA; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Barts Cancer Centre, Queen Mary University of London, London, United Kingdom; Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; Genentech, Inc., South San Francisco, CA; Path AI, Boston, MA; Genentech Inc, South San Francisco, CA

Background: Metastatic RCC (mRCC) is a molecularly heterogeneous disease. Transcriptomic analysis in the Phase 3 IMmotion 151 (Im151) trial identified 7 molecular subtypes that showed differential outcomes to Atezolizumab+Bevacizumab (A+B) vs Sunitinib (S) treatment (Motzer, Cancer Cell 2020). Here, we present histological correlates of these subtypes as identified in whole slide images (WSI) of hematoxylin and eosin (H&E) stained tumors. **Methods:** ML models identified 922 H&E derived, human interpretable histological features (ML HIFs) in RCC associated with tumor and stromal (including vessels, immune cells, fibroblasts) cell and tissue morphologies, and nucleus shape. These ML HIFs were then extracted from WSI in 2 mRCC trials – Im151 (n=797) and IMmotion150 (Im150, n=203). Previously described 7 molecular subtypes were combined into 4 subgroups (Angiogenic [comprised of Angiogenic/Stromal and Angiogenic], Complement/OmegaOxidation, T-effector, and Proliferative [comprised of Proliferative and Stromal Proliferative]) for computational power. Due to low prevalence, snoRNA subset was excluded. Univariate analysis with FDR correction was applied to identify positively associated ML HIFs in each of the 4 subgroups in the Im151 WSI and then validated in Im150 subgroups. Representative ML HIFs that showed uniquely higher abundance in each molecular subgroup in both studies were dichotomized by tertiles as 'high' or 'low/intermediate' and associated with progression free survival (PFS) to fit Cox proportional hazard models in Im151 study. **Results:** 169 ML HIFs were differentially enriched across 3 molecular subgroups in both Im151 and Im150 data sets. Angiogenic subgroup had higher prevalence of 40 ML HIFs associated with density of endothelial cells in cancer epithelium. T-effector subtype showed higher abundance of 64 ML HIFs associated with immune cell presence in stroma. Proliferative subgroup showed higher prevalence of 40 ML HIFs associated with nuclear morphologies. No ML HIFs were uniquely associated with the Complement/OmegaOxidation subgroup. Consistent with transcriptional findings in Im151, ML HIFs that were enriched in T-effector and Proliferative subgroups showed improved PFS benefit to A+B vs S (Table). **Conclusions:** We identified unique histological features of RCC tumors that correlate with previously defined molecular subtypes. Our results suggest that clinically relevant RCC subtypes may be extracted directly from H&E-stained WSI and may complement gene expression based patient stratification and selection strategies. Research Sponsor: F. Hoffmann-La Roche Ltd.

Molecular Subgroup	ML HIF Description	A+B vs S PFS HR (95% CI)
Angiogenesis	Density of endothelial cells in tumor tissue	1.14 (0.85-1.54)
T-effector	Density of lymphocytes in cancer epithelium	0.72 (0.54-0.97)
Proliferative	Mean length of clear cell tumor cell nucleus perimeter	0.62 (0.47-0.83)

Comparing the somatic, germline, and immune landscapes of upper tract urothelial carcinoma (UTUC) and UC of the bladder (UCB).

Kit L. Yuen, Margaret F. Meagher, Jacob Mercer, Binyam Yilma, Melissa Conrad Stoppler, Stamatina Fragkogianni, Nataliya Mar, Arash Rezazadeh, Shilpa Gupta, Petros Grivas, Aditya Bagrodia, Rana R. McKay, Tyler F. Stewart, Amirali Salmasi; University of California, San Diego Health, La Jolla, CA; Tempus AI, Chicago, IL; University of California, Irvine Medical Center, Orange, CA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; University of California, San Diego, La Jolla, CA

Background: Molecular characterization of anatomically distinct UCs has been limited by the rarity of UTUC; however, recent advances in real-world data curation have enabled larger UTUC cohort generation. Here, we investigated the somatic, germline, and immunologic landscapes of UTUC compared to UCB. **Methods:** From the Tempus Database, we retrospectively analyzed de-identified next-generation sequencing data from 505 UTUC (224 ureter, 281 renal pelvis) and 2,416 UCB cases (2,379 bladder, 37 urethra). Tumors were sequenced with the Tempus xT DNA and xR RNA assays. Pathogenic somatic mutations, immune cell infiltration predicted from gene expression patterns, TMB, PD-L1 from IHC, MSI, and mismatch repair (MMR) were evaluated. Incidental germline alterations were assessed in 46 genes for patients with tumor/normal-matched (T/N) sequencing (UTUC n=285, UCB n=1,359). Chi-squared, Fisher's exact, and Wilcoxon rank-sum tests were used to assess statistical significance ($p<0.05$, $q<0.05$ for false discovery rate correction for multiple testing). **Results:** Median age of the UTUC and UCB cohort were 73 and 70 years, respectively (p=0.003). The UCB cohort had significantly more males (75% vs 56%, $p<0.001$) and ever smokers (59% vs 46%, $p<0.001$).Alterations in *TERT*, *TP53*, *CDK12*, *RB1*, *ERBB2*, and *CDKN1A* were more frequent in UCB, while *KMT2D*, *FGFR3*, *BRIP1*, *CDKN2B*, *KRAS*, and *MYC* more frequent in UTUC (Table). Additionally, *FGFR3* fusions were more frequent in UTUC. Germline variants were found in 7.1% of UCB and 7.0% of UTUC cases, with trends towards higher prevalence of alterations in lynch-associated genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) in UTUC (0.6% vs 1.8%, p=0.059). The prevalence of TMB ≥ 10 mut/Mb was higher in UCB vs UTUC (17% vs 11%, $p<0.001$). UCB had increased PD-L1 positivity (p=0.013), whereas UTUC had more MSI-high (UTUC = 3.2% vs UCB = 1%, p=0.001) and deficient MMR (p=0.020) cases. There were similar proportions of total immune infiltrates in UCB and UTUC. However, UTUC harbored a higher percentage of CD4+ T cells ($p<0.001$), while UCB had a higher proportion of regulatory T and NK cells ($p<0.001$). **Conclusions:** Via comprehensive molecular characterization of UC, we observed distinct DNA alteration and tumor microenvironment patterns in UTUC and UCB. The germline results underline how T/N testing can identify patients with UTUC and/or UCB who can benefit from dedicated germline testing. Further research is warranted to elucidate the clinical implications of these findings. Research Sponsor: Tempus AI, Inc.

Molecular Characteristic	UCB (n = 2,416)	UTUC (n = 505)
TERT*	76%	52%
KMT2D*	22%	36%
RB1*	22.0%	8.9%
FGFR3*	13%	21%
CDK12*	5.0%	1.4%
TP53*	59%	51%
ERBB2*	14.0%	8.3%
***FGFR3* fusions**[†]	4.0%	6.1%

*% mutated, $q<0.05$; [†]$p<0.05$; [‡]$p< 0.001$; Analysis included short variants and copy number variants with the exception of *FGFR3* fusions.

Impact of Latino ethnicity on the gut microbiome composition of patients with metastatic renal cell cancer (mRCC).

Regina Barragán Carrillo, Nazli Dizman, Hedyeh Ebrahimi, Luis A Meza, Paulo Gustavo Bergerot, Tanya B. Dorff, Joann Hsu, Zeynep Busra Zengin, Nicholas Salgia, Alex Chehrazi-Raffle, Abhishek Tripathi, Daniela V. Castro, Benjamin Mercier, Gregory Caporaso, Keehoon Lee, Sumanta Kumar Pal; City of Hope Comprehensive Cancer Center, Duarte, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Yale University School of Medicine, New Haven, CT; Oncoclinicas & Co - Medica Scientia Innovation Research (MEDSIR), São Paulo, Brazil; Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Translational Genomics Institute, Phoenix, AZ; Translational Genomics Research Institute (TGen North), Flagstaff, AZ

Background: Latinos with mRCC may have poorer outcomes with frontline immune checkpoint inhibition (ICI) compared to their non-Latino counterparts (Chehrazi-Raffle *et al*Oncologist 2023). Recent studies have shown that the composition of the gut microbiome can impact outcomes with ICI (Routy *et al*Science 2018). Therefore, we aimed to investigate the differences in gut microbiome composition between Latino and non-Latino patients (pts) with mRCC. **Methods:** Stool specimens were prospectively collected in treatment-naïve pts with mRCC. We dichotomized pts into Latino vs non-Latino groups. Pts provided a stool sample (OMNIgene Gut) at baseline. Whole metagenome sequencing was performed on stool specimens collected. Taxonomic profiling was conducted using MetaPhlAn 4. ANCOM-BC analysis was used to identify differences in the relative abundance of bacterial species between groups. Alpha-diversity was evaluated using the Shannon diversity index and Evenness analysis, employing the Kruskal-Wallis test. Beta-diversity was assessed using the Bray-Curtis and Jaccard dissimilarity measures. The ratio of Firmicutes/Bacteroidetes (F/B), a measure of gut dysbiosis, was computed at baseline in the two cohorts. **Results:** Among 59 pts assessed, 27 and 32 were Latino and non-Latino, respectively. Median age of the cohort was 60 (range, 36-90). Most were male (71%), had clear cell RCC (88%) and had intermediate/poor risk disease (79%). ANCOM-BC analysis showed an enrichment of 14 bacterial species and a depletion in 3 species at baseline in the Latino group ($p \leq 0.05$). Three *Roseburia*spp. were enriched in the Latino pts, namely *R. faecis* (log-fold change [LFC]: 2.6), *R. hominis* (LFC: 2.0) and *R. inulinivorans* (LFC: 1.8). Additionally, *Eubacterium rectale*was also enriched in the Latino group (LFC: 2.0). In contrast, in non-Latino pts *Methylobacterium* spp. was enriched (LFC: 1.3). The F/B ratio was higher in the Latino group as compared to the non-Latino group (1.00 vs 0.92). We did not observe any differences in alpha and beta diversity. A detailed analysis of simultaneously collected dietary logs is ongoing. **Conclusions:** Our examination of the gut microbiota of pts with mRCC revealed significant differences based on ethnicity at baseline. Specifically, the Latino group exhibited an enhancement of *Roseburia spp.* and *E. rectale*, species previously linked to favorable outcomes with ICIs, despite a higher F/B ratio (suggesting a greater degree of dysbiosis). Our findings advocate that clinical trials related to the microbiome should potentially account for baseline differences in ethnicity. Research Sponsor: None.

4522 Poster Session

Multi-omics analyses and molecular subtypes to provide potential therapeutic implications in fumarate hydratase-deficient renal cell carcinoma.

Xingming Zhang, Junjie Zhao, Xiaoxue Yin, Jiayu Liang, Yongquan Wang, Linmao Zheng, Ping Tan, Sha Zhu, Junru Chen, Jinge Zhao, Niels J Rupp, Xinan Sheng, Qiang Wei, Xiang Li, Jin Yao, Zhenhua Liu, Pengfei Shen, Ni Chen, Hao Zeng, Guangxi Sun; Department of Urology, Institute of Urology, Sichuan Clinical Research Center for Kidney and Urologic Diseases, West China Hospital, Sichuan University, Chengdu, China; Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; Department of Pathology, West China Hospital, Sichuan University, Chengdu, China; Department of Urology, Southwest Hospital, Army Medical University, Chongqing, Chengdu, China; West China Hospital, Sichuan University, Chengdu, China; Department of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland; Department of Genitourinary Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China

Background: Fumarate hydratase-deficient renal cell carcinoma (FH-deficient RCC) is a rare yet highly lethal kidney cancer. To deepen our understanding of FH-deficient RCC, we conducted a comprehensive integrated genomic study. **Methods:** A total of 126 treatment naïve FH-deficient RCC tissue samples were extracted from our multi-center database. Whole-exome, RNA-seq, and DNA-methylation sequencing were performed. All cases were confirmed with both FH/2SC immunohistochemical staining and FH alterations analysis. **Results:** Through whole-exome sequencing, we found FH alteration patterns were associated with both tumor behavior and patient survival outcomes. Tumors harboring FH truncating alteration (including nonsense, frameshift and splice site mutations) and mutations near hinge regions (such as p.S419L), were predominantly associated with more aggressive tumor behavior and poorer prognosis. We further developed a CpG sites-specific methylation signature for precise identification of FH-deficient RCC. More importantly, transcriptomic analysis unveiled three distinctive molecular subtypes characterized by enrichment of immune/Angiogenic/Stromal (C1), WNT/Notch/MAPK (C2), and proliferation/stemness (C3) pathways, respectively. Tumors in C1 derived the most substantial survival benefit from a combination of immune checkpoint blockade (ICB) and anti-angiogenic therapy. Tumors in C2 displayed moderate response to this therapeutic approach. In contrast, tumors in C3 exhibited an unfavorable response to anti-angiogenic monotherapy and its combination with ICB. **Conclusions:** These findings contribute to a profound understanding of the aggressive nature of FH-deficient RCC, offering insights into potential precision medicine approaches for disease management. Research Sponsor: None.

Sintilimab plus axitinib for advanced fumarate hydratase-deficient renal cell carcinoma: A multi-center, open-label, single-arm, phase II study (SAFH).

Hao Zeng, Xingming Zhang, Jiayu Liang, Junjie Zhao, Haoyang Liu, Yaowen Zhang, Yuntian Chen, Guangxi Sun, Xinan Sheng, Yongquan Wang, Xiaodong Liu, Rui Huang, Qiang Wei, Xiang Li, Jiyan Liu, Pengfei Shen, Pengfei Shen, Ni Chen, Jin Yao, Zhenhua Liu; Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; West China Hospital, Sichuan University, Chengdu, China; Department of Radiology, West China Hospital, Sichuan University, Chengdu, China; Peking University Cancer Hospital and Institute, Beijing, China; Department of Urology, Southwest Hospital, Army Medical University, Chongqing, Chengdu, China; The First Affiliated Hospital of Kunming Medical University, Kunming, China; Department of Nuclear medicine, West China Hospital, Sichuan University, Chengdu, China; Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Department of Pathology, West China Hospital, Sichuan University, Chengdu, China

Background: Fumarate hydratase-deficient renal cell carcinoma (FH-dRCC) is a rare and highly invasive subtype of renal cell carcinoma. Previous studies have shown that immune checkpoint inhibitor (ICI) plus tyrosine kinase inhibitor (TKI) can be considered for first-line systemic treatment of FH-dRCC. We aimed to provide high-quality prospective clinical trial evidence regarding the efficacy and safety of Sintilimab plus Axitinib in FH-dRCC. **Methods:** This study was an investigator-initiated, open-label, single-arm, multiple institutional, phase II trial in patients (pts) aged 18 years or older with treatment naive, advanced FH-dRCC. Patients received Sintilimab (intravenous injection, every 3 week) in combination with Axitinib (5mg, orally taken per day) as first-line treatment until disease progression or intolerant to treatment. The primary endpoint was objective response rate (ORR; RECIST v1.1) and progression-free survival (PFS). This study is registered with ClinicalTrials.gov, NCT04387500. **Results:** From June 2021 to August 2023, 52 patients were screened, and 41 patients were enrolled. The median follow up was 16.0 months. Thirty-eight patients were available for efficacy assessment. Confirmed complete response rate was 10.5% (4/38), ORR was 60.5% (23/38). Disease-controlled rate (DCR) was 86.8%. The median PFS was 19.83 months (95% CI: 7.68-31.99). All grade and $\geq$3 treatment-emergent adverse events occurred in 87.8% (36/41) and 22.0% (9/41), respectively. Details about FH mutation status were available in 40 patients, and different FH mutation patterns were found to be associated with different therapeutic efficacy. **Conclusions:** The combination of Sintilimab and Axitinib showed manageable safety profile and durable anti-tumor efficacy in FH-dRCC. Evaluating mutation status of FH gene could help to predict potential survival benefit from ICI plus TKI therapy. Clinical trial information: NCT04387500. Research Sponsor: None.

Lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in advanced renal cell carcinoma (aRCC): Patterns of progression and subsequent therapy in the CLEAR trial.

Viktor Grünwald, Robert J. Motzer, Daniel Keizman, Jens Bedke, Manuela Schmidinger, Michael D. Staehler, Vsevolod B. Matveev, Saby George, Thomas E. Hutson, Ulka N. Vaishampayan, Jaime R. Merchan, Masatoshi Eto, Sun Young Rha, Tom Waddell, Roberto Sabbatini, Philippe Barthelemy, Joseph E. Burgents, Min Ren, Ian Brown, Toni K. CHOUEIRI; University Hospital Essen, Essen, Germany; Memorial Sloan Kettering Cancer Center, New York, NY; Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; Department of Urology and Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; Medical University of Vienna, Vienna, Austria; University Hospital of Munich, Munich, Germany; State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; Roswell Park Cancer Institute, Buffalo, NY; Texas Oncology, Dallas, TX; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Kyushu University, Fukuoka, Japan; Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; The Christie NHS Foundation Trust, Manchester, United Kingdom; University Hospital of Modena, Modena, Italy; Strasbourg European Cancer Institute, Strasbourg, France; Merck & Co., Inc., Rahway, NJ; Eisai Inc., Nutley, NJ; Eisai Ltd., Hatfield, United Kingdom; Dana-Farber Cancer Institute, Boston, MA

Background: In the primary analysis of the CLEAR trial of patients (pts) with aRCC, L+P significantly improved efficacy vs S (Motzer NEJM 2021). Results were further confirmed at the final prespecified OS analysis (Motzer JCO 2024). Here, we discuss patterns of progression and subsequent therapy in CLEAR. **Methods:** Treatment-naïve pts (n=1069) who had aRCC with a clear-cell component were randomly assigned (1:1:1) to receive: L 20 mg PO QD + P 200 mg IV Q3W; or L 18 mg + everolimus 5 mg PO QD; or S 50 mg PO QD (4 wks on/2 wks off). Stratification factors were region and MSKCC prognostic risk group. To explore progression pattern within individual organs, time to progression was defined for each organ independently using lesions within each specific organ only, based on Independent Image Review per RECIST v1.1. Medians and quartiles were estimated with Kaplan-Meier (KM) method; 95% CIs were estimated with a generalized Brookmeyer and Crowley method. Hazard ratio (HR) reported is for L+P vs S based on Cox regression model with treatment as factor; HR was stratified by region and MSKCC prognostic groups. The Efron method was used for correction for ties. **Results:** The HRs (95% CI) of time to progression for L+P vs S across tumors in different organs were: bone, 0.40 (0.25-0.63); CNS, 0.47 (0.19-1.19); kidney, 0.65 (0.37-1.14); liver, 0.52 (0.32-0.84); lung, 0.48 (0.36-0.62); and lymph nodes, 0.63 (0.46-0.85). At overall disease progression, the median sums of diameters of target lesions were lower with L+P vs S (29.8mm vs 42.8mm; Table). In the L+P arm, 181 pts received subsequent anticancer regimens during survival follow-up (43 received axitinib and 101 received cabozantinib). In the S arm, 246 pts received subsequent anticancer regimens (47 received axitinib and 107 received cabozantinib). The median duration of axitinib as the first anticancer regimen (95% CI) after L+P was 23.7 months (5.3-not estimable [NE]), and after S was 12.6 months (6.8-NE). The median duration of cabozantinib as the first anticancer regimen (95% CI) after L+P was 13.2 months (8.2-NE), and after S was 7.1 months (4.1-20.0). **Conclusions:** Pts in the L+P arm trended to show later progression across tumors in different organs. At overall disease progression, the tumor burden of target lesions was lower with L+P vs S; and pts in the L+P arm stayed on 2L axitinib or cabozantinib longer than pts in the S arm. Together, these results continue to support L+P as a standard-of-care 1L therapy in pts with aRCC. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	L+P (n = 355)	S (n = 357)
Pts with progressive disease and target lesions at baseline, n	176	195
Baseline sums of target lesion diameters (mm) Median (Q1, Q3)	56.7 (32.8, 117.0)	56.7 (38.2, 97.6)
Sums of target lesion diameters (mm) at progression Median (Q1, Q3)	29.8 (12.2, 66.1)	42.8 (24.6, 84.3)
Change in sums of target lesion diameters from baseline (%) Median (Q1, Q3)	−48.1 (−71.1, −26.3)	−17.4 (−40.3, 0.8)

CA-62: A new biomarker for the detection of early-stage renal cell carcinoma.

Janneta Tcherkassova, Sergei Tsurkan, Anna Prostyakova, Evgueni Klinski, Marina Sekacheva, Alexander Boroda, Ricardo Moro; UCM Technologies Inc., Toronto, ON, Canada; Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russian Federation; IM Sechenov First Moscow State Medical University, Moscow, Russian Federation; Pacific Biosciences Research Centre, Richmond, BC, Canada

Background: The American Cancer Society classifies Renal Cell Carcinoma (RCC) to be among the ten most common cancers. However, in spite of this need, effective biomarkers for early-stage detection of RCC are not yet available. The purpose of this study was to assess the diagnostic characteristics of a carcinoma-specific transmembrane N-glycoprotein biomarker, CA-62, for the detection of early-stage kidney cancer. Blinded serum samples from 204 patients were included in the clinical study, of which 68 had TNM-classified stages IA, IB, IIA or IIB renal cell carcinomas, while 136 were drawn from healthy volunteers. **Methods:** Quantitative measurement of serum CA-62 levels was performed using a chemiluminescent immunoassay (''JVS Diagnostics'' LLC). Statistical analysis (MedCalc; version 19.7.4, MedCalc Software Ltd, Belgium, EU) was used to assess the diagnostic characteristics of the CA-62 biomarker for detection of RCC, including sensitivity and specificity, and test accuracy. **Results:** Significantly higher median concentrations of CA-62 were found in sera of RCC patients compared to those found in healthy controls as follows; stage I A, B (8,935 U/mL), stage II A (6,291 U/mL), stage II B (8,808 U/mL), and healthy controls (2,815 U/mL). It was expected that serum CA-62 levels would be elevated at these early stages of RCC (Stages I-IIB), demonstrating significant overexpression of this epithelial carcinoma marker during the initial stages of cancerogenesis. The results of the study are presented in the table. Area under the ROC curve (AUC) for RCC patients vs. healthy controls was 0.98 with a 95% CI (0.950-0.994), z-statistics (67.3), and a significance of $p<0.0001$. **Conclusions:** CA-62 demonstrated a 94.3% sensitivity for RCC at 96% specificity during the early stages of kidney cancer. Given that CA-62 is not specific for kidney cancer, it is reasonable to suggest that use of a combination of CA-62 with some other biomarkers that may lack the sensitivity of CA-62 but are often elevated in renal cell carcinoma patients, such as tumor-infiltrating lymphocytes and/or possibly some inflammation biomarkers. In particular, the combination of transmembrane glycoproteins CA-62 and CD105, combined with biomarkers such as Endothelial Vascular Growth Factor (EVGF) and/or a growth factor derived from platelets (PDGF) could be successfully used for kidney cancer screening in order to achieve both high sensitivity and specificity for RCC detection. Research Sponsor: None.

Diagnostic characteristics of CA-62 for patients with early stages of RCC.

Parameter	Number of Patients With CA-62 > 5000 U/mL, %
Stage I A, B	48/51 (94%)
Stage I A	28/31 (90%)
Stage I B	20/20 (100%)
Stage II A, B	16/17 (92%)
Stage II A	12/13 (92%)
Stage II B	4/4 (100%)
Total	64/68 (94.3%)
Healthy volunteers	5/136 (4%)
Sensitivity %	94.3%
Specificity %	96%
AUC	0.98
Test Accuracy %	95.5%

Changes in treatment (Rx) patterns and attrition rates in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC).

Gliceida Galarza Fortuna, Yeonjung Jo, Chadi Hage Chehade, Arshit Narang, Georges Gebrael, Vinay Mathew Thomas, Beverly Chigarira, Ethan Anderson, Archisman Mazumder, Zeynep Irem Ozay, Neeraj Agarwal, Benjamin L. Maughan, Umang Swami; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; University of Utah/Huntsman Cancer Institute, Salt Lake City, UT; Gazi University Faculty of Medicine, Ankara, Turkey; Huntsman Cancer Institute, Salt Lake City, UT

Background: Rx landscape of mccRCC has evolved rapidly with the approval of antibodies directed against programmed cell death protein-1 (PD-1) in combination with cytotoxic T-lymphocyte-associated protein 4 (CTLA4) or vascular endothelial growth factor receptor tyrosine kinase (TKI) inhibitors. However, real-world data on Rx trends and attrition before and after PD-1 inhibitor approval are lacking. Herein, we analyze them in a large real-world cohort in the United States. **Methods:** This IRB-approved retrospective study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. Inclusion: Metastatic RCC with clear cell histology diagnosed between 1/1/2011 to 1/31/2022 receiving Rx with opportunity of at least 1 year follow up. Exclusion: Pts needing Rx for ≥2 malignancies. Based on the approval date of PD-1+CTLA4 of 4/16/18, pts were separated into 2 groups: b2018 (1L Rx before 4/16/2018) and a2018 (1L Rx after 4/16/18). Landmark analysis was performed at 1 year after Rx discontinuation to identify pts who died, were alive but did not need Rx, or starting next-line Rx. All analysis was done using R version 4.2.3. **Results:** Of 12707 pts, 7923 met the eligibility criteria (b2018: 4561 pts and a2018: 3362 pts). Rx trends are summarized in the table. 1L Rx for the majority of pts changed from TKI monotherapy (mono; 79%) b2018 to PD-1 combination therapies a2018 (58%). TKI mono remained the most common Rx in both groups after 1L (Table). In the b2018 cohort, 58% of patients received 2L Rx, and 32% received 3L. In the a2018 cohort, 42% and 16% received 2L and 3L, respectively. At 1-year landmark analysis after 1L discontinuation: in the b2018 group, 58% pts received next Rx, 30% died without further Rx, and 12% were alive without Rx while in the a2018 group, 42% pts received next Rx, 26% died without further Rx and 32% were alive without Rx. **Conclusions:** Despite the increase in the utilization of PD-1+CTLA-4 and PD-1+TKI regimens since 2018, a significant number of patients still did not receive novel combination regimens in the 1L mccRCC setting in this real-world population in the United States. Furthermore, with the uptake of PD-1 based combinations in 1L, a higher proportion of pts experience treatment free interval or were alive without further therapy at 1 year landmark analysis after 1L Rx discontinuation. These findings need validation in other datasets and can help patient counseling in clinics. Research Sponsor: None.

Rx trends for mccRCC.

Rx	1L b2018 n (%)	1L a2018 n (%)	2L b2018 n (%)	2L a2018 n (%)	3L b2018 n (%)	3L a2018 n (%)
Overall	4561	3362	2639	1408	1458	551
TKI	3595 (79%)	880 (26%)	1029 (39%)	630 (45%)	688 (47%)	285 (52%)
PD-1+CTLA-4	26 (0.6%)	1079 (32%)	69 (3%)	113 (8%)	48 (3%)	37 (7%)
PD-1+TKI	23 (0.5%)	862 (26%)	86 (3%)	356 (25%)	75 (5%)	123 (22%)
PD-1	170 (4%)	475 (14%)	807 (31%)	251 (18%)	340 (23%)	49 (9%)
Others	747 (16%)	66 (2%)	648 (25%)	58 (4%)	307 (21%)	57 (10%)

Comparison of TKI and CPI strategies as first-line treatment of patients with advanced renal cell carcinoma: Real-world outcome data from the German research platform CARAT.

Peter J. Goebell, Martin Boegemann, Arnd Nusch, Viktor Grünwald, Lothar Mueller, Eyck von der Heyde, Dietmar Reichert, Uwe Marc Martens, Carolin Lennartz, Michaela Koska, Martina Jänicke, Karin Potthoff, Norbert Marschner, Carsten Grüllich, Michael D. Staehler; University Clinic Erlangen, Erlangen, Germany; Department of Urology, Münster University Medical Center, Münster, Germany; Practice for Hematology and Internal Oncology, Velbert, Germany; Clinic for Internal Medicine (Tumor Research) and Department of Urology, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany; Oncological Practice UnterEms, Leer, Germany; Onkologie am Raschplatz, Hannover, Germany; Gemeinschaftspraxis für Hämatologie und Onkologie, Westerstede, Germany; SLK-Kliniken Heilbronn, Clinic for Internal Medicine, Heilbronn, Germany; iOMEDICO, Freiburg, Germany; Universitätsklinikum Freiburg, Freiburg, Germany; Sana Klinikum Hof, Hof, Germany; University Hospital of Munich, Munich, Germany

Background: Immune checkpoint inhibitors (CPI), in combination with tyrosine kinase inhibitors (TKI) or with another CPI, expanded the therapeutic options for advanced or metastatic renal cell carcinoma (mRCC) beyond TKI-Monotherapy. However, no head-to-head clinical trials comparing 1st-line (1L) CPI+CPI vs. TKI+CPI have been performed. Here, we analyzed outcome of non-randomized patients (pts) treated 1L with one of the three strategies in routine care. **Methods:** CARAT (NCT03374267) is an ongoing, prospective, observational, longitudinal, multicenter clinical registry for mRCC pts in Germany. Details on (sequential) treatments, patient and tumor characteristics and clinical and patient-reported outcomes are collected. Follow-up is until death or up to 3 years. By January 2024, almost 1100 pts had been enrolled by 148 sites. Pts with start of 1L treatment after 15/01/2019 were analyzed (data cut 06/30/2023). PFS and OS were estimated using the Kaplan-Meier method. Inverse probability of treatment weighting (IPTW) by propensity score analysis was used to compare PFS (primary endpoint) and OS (secondary endpoint) between 1L TKI or CPI+CPI or TKI+CPI. IPTW was performed for the following variables: age, sex, IMDC risk groups, histology, any comorbidity, Charlson comorbidity index, metastatic stage, type of metastasis and number of metastatic sites. After IPTW, the three treatment groups were comparable for the variables listed above. **Results:** From 2019 until data cut for this analysis, 991 pts were investigated, thereof 418 pts (42%) received TKI+CPI, 242 pts (24%) CPI+CPI and 263 pts (27%) received TKI monotherapy as 1L. 51/61/80% of pts had a progression or death after 1L (TKI+CPI/CPI+CPI/TKI strategy group). IPTW-adjusted median PFS was 12.7 months (95% confidence interval (CI) [10.4 – 15.6]) for TKI+CPI, 8.0 [6.3 – 10.9] months for CPI+CPI and 9.7 [7.4 – 12.0] months for TKI. Hazard ratio (HR) was 1.24 (0.97 – 1.58) for CPI+CPI versus TKI+CPI and 1.33 (1.09 – 1.61) for TKI versus TKI+CPI. 30/42/51% of pts had died (TKI+CPI/CPI+CPI/TKI strategy group). IPTW-adjusted median OS was 31.5 [26.4 – NA] months for TKI+CPI, 22.3 [17.1 – 37.5] months for CPI+CPI and 31.4 [22.8 – 37.1] months for TKI. HR was 1.30 (0.98 – 1.73) for CPI+CPI versus TKI+CPI and 1.08 (0.83 – 1.41) for TKI versus TKI+CPI. Subgroup analyses by IMDC score as well as data on quality of life and on subsequent line treatments will also be presented. **Conclusions:** IPWT-adjusted outcome analysis of real-world data in the CARAT registry did not detect significant differences in PFS and OS between pts treated with 1L TKI+CPI compared to CPI+CPI when adjusted for a wide range of potential confounding variables. Further analyses in other cohorts are warranted to confirm these findings. Research Sponsor: None.

First-line systemic therapy following adjuvant immunotherapy in renal cell carcinoma (RCC): An international multi-center study.

Talal El Zarif, Karl Semaan, Wanling Xie, Charles B Nguyen, Catherine Fahey, Martin Zarba, Anezka Zemankova, Hedyeh Ebrahimi, Giuseppe Procopio, Marco Stellato, Sebastiano Buti, Bohuslav Melichar, Balaji Venugopal, Jose A. Karam, Matthew T Campbell, Katy Beckermann, Ajjai Shivaram Alva, Sumanta Kumar Pal, Daniel Yick Chin Heng, Toni K. CHOUEIRI; Department of Internal Medicine, Yale University School of Medicine, New Haven, CT; Dana-Farber Cancer Institute, Boston, MA; Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA; Rogel Comprehensive Cancer Center, Ann Arbor, MI; Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; Tom Baker Cancer Centre, University of Calgary, Alberta, Canada; Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic; City of Hope Comprehensive Cancer Center, Duarte, CA; Genitourinary Medical Oncology, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; Campus Biomedico, Roma, Italy; University Hospital of Parma, Fontevivo, Italy; Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, United Kingdom; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Vanderbilt University Medical Center, Nashville, TN; Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Adjuvant pembrolizumab significantly improved overall survival (OS) and is FDA-approved for adjuvant RCC treatment. However, there is a paucity of data on sequential treatment following recurrence after pembrolizumab or other immune-oncology (IO)-based therapies (PD-1 or PD-L1 inhibitors) administered in the adjuvant setting. **Methods:** This study included consecutive patients (pts) from 27 international centers who received adjuvant IO-based systemic RCC therapies. Safety and efficacy of subsequent systemic therapy regimens that included vascular endothelial growth factor-targeted therapies (VEGF-TT) or alternative IO-based therapies were evaluated. Progression-free survival (PFS) and OS from the time of systemic therapy initiation following adjuvant IO were estimated using the Kaplan-Meier method. Objective response rates (ORRs) were determined per RECIST 1.1 criteria. Treatment-related adverse events (trAEs) leading to treatment discontinuation, dose reduction, or steroid use were collected. **Results:** Among 144 pts who received adjuvant IO, median (Q1-Q3) age was 56 (50-64) years, and 105 (73%) were males. Most pts had clear cell RCC (n=130, 90%), underwent radical nephrectomy (n=136, 94%), and had high or intermediate-high risk disease (n=129, 90%) per KEYNOTE-564 risk groups. Tumors of 15 (10%) pts had sarcomatoid features. Most pts received adjuvant pembrolizumab (n=74, 51%), atezolizumab (n=40, 28%), or nivolumab plus ipilimumab combination therapy (n=16, 11%). Most common reasons for adjuvant IO cessation were treatment completion (n=65, 45%), recurrence (n=36, 25%), or toxicity (n=34, 24%). RCC did not recur in 52 (36%) pts who remained under observation, whereas 92 (64%) had recurrent disease. Following tumor recurrence, 69/92 (75%) pts received systemic therapy; the remaining 25% underwent surgery or radiotherapy. Median follow-up from systemic therapy initiation was 16.7 months. Median PFS was 16 months (95% CI = 10.4 – 41.7), and 18-month OS was 86% (95%CI: 76.4 – 97.3%). ORR was 36% (n = 25/69). Most pts received VEGF-TT (n=32, 46%), IO/VEGF-TT combinations (n=21, 30%), or single/combination IO (n=12, 17%). ORRs were comparable (35% in VEGF-TT monotherapy, 45% in IO/VEGF-TT combination, 42% in single/combination IO cohort). In 23 pts who received adjuvant pembrolizumab monotherapy and subsequent systemic therapy, ORR was 44% (4/9) vs. 29% (4/14) for those recurring after vs. prior to discontinuation of pembrolizumab, respectively. Two out of 8 pts who discontinued adjuvant IO due to toxicity were rechallenged with subsequent IO and had stable disease, and one of them developed an immune-related AE. TrAEs occurred in 28/69 (41%) pts treated with subsequent systemic therapy. **Conclusions:** Patients with RCC who recur on or after adjuvant IO treatment benefit from subsequent systemic therapies across different regimens. Research Sponsor: None.

Tumor evolution of brain-specific tropism in metastatic renal cell carcinoma.

Roy Elias, Ardit Feinaj, Aparna Pallavajjala, Anirudh Yerrapragada, Max Drescher, Sunil H. Patel, Elana J. Fertig, David Kamson, Mark Christopher Markowski, Srinivasan Yegnasubramanian, Andres Matoso, Ezra Baraban, Chetan Bettegowda, Yasser Ged, Nirmish Singla; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; JHU, Baltimore, MD; Johns Hopkins, Baltimore, MD; University of Maryland, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Johns Hopkins Brain Tumor Group, Baltimore, MD; Johns Hopkins Hospital, Baltimore, MD; Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, MD; Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; The James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, MD

Background: Brain metastases (BMets) pose a clinical challenge in the management of patients (pts) with metastatic renal cell carcinoma (RCC), leading to significant morbidity and mortality. Herein, we sought to comprehensively characterize the molecular landscape of BMets in RCC. **Methods:** We performed panel-based DNA (DNAseq) and whole transcriptome (RNAseq) sequencing to analyze BMets, matched non-Brain metastases (nBMets), and matched primary renal tumors (PRT) from pts who underwent surgical resection of BMet(s) from RCC at our institution. **Results:** Our cohort consisted of 95 samples from 53 patients (BMets = 54, nBMets = 14, PRT = 27) with clear cell histology in 45 pts (84.9%). DNAseq was available 85 samples (50 pts). Patient-level mutations revealed recurring mutations in *VHL*(18 pts, 36%), *TP53* (n = 12 pts, 24%), *PBRM1*(12 pts, 24%), *SETD2*(12 pts, 24%), and *BAP1*(4 pts, 8%). Mutations within the MTOR signaling pathway were enriched, with 25 pts (50%) having at least one mutation in *PTEN* (12 pts, 24%), *TSC1* (4 pts, 8%), *TSC2* (5 pts, 10%), or *MTOR* (9 pts, 18%). Copy number analyses revealed frequent deletions in chr14q21 (34 pts, 68%) and chr9p21 (35 pts, 70%) and gains in chr20q13 (n = 31, 62%) and chr7p15 (n = 31, 62%). At the sample-level, *PTEN* mutations were more common in BMets (11 pts, 22.9%) vs nBMets (0 pts) and PRTs (3 pts, 12%, p = 0.124), as were deletions in chr13q22 (BMets = 13pts [26.5%], nBMet = 1pts [8.3%], PRT = 1 [4%]; p = 0.036) and gains in chr20q13 (BMets = 30pts [61.2%], nBMet = 4pts [33.3%], PRT = 8 [32%]; p = 0.03). Deletions in chr9p21 were enriched in BMets (32, 65.3%) and nBMets (8, 66.7%) relative to PRTs (7, 28%, p = 0.006), whereas other copy number alterations and somatic mutations exhibited similar proportions across specimen sites. Differential expression analysis performed on 86 samples (51 pts) identified 806 differentially expressed genes (DEGs) between BMets and PRT (adjusted [adj.] $p < 0.05$) and 399 DEGs between BMet and nBMets (adj. $p < 0.05$). Gene set enrichment analysis of MSigDB Hallmark gene sets revealed upregulation of MTORC1 signaling, glycolysis, and MYC targets in BMets comparted to PRT and nBMETs (adj. $p < 0.0001$). In contrast, immune-related gene sets, such as interferon-alpha, interferon-gamma, and tumor necrosis factor-alpha, were enriched in PRT relative BMets (adj. $p < 0.0001$), but not nBMETs (adj. $p > 0.05$). CIBERSORT cellular deconvolution analysis comparing BMets with PRT revealed decreased proportions of M1 macrophages (p = 0.0003) and CD8+ T-cells (p = 0.0106), but an increase proportion of M2 macrophages (p = 0.0009). **Conclusions:** RCC with brain metastases are characterized by distinct copy number alterations, enrichment of MTOR pathway mutations, MTOR pathway hyperactivation, and an immunosuppressive tumor milieu. These findings may hold therapeutic implications of MTOR pathway inhibition and immune modulators in treating RCC BMets. Research Sponsor: Kidney Cancer Association; American Urological Association Urology Care Foundation; Conquer Cancer, the ASCO Foundation.

Leukocyte immunoglobulin-like receptor (LILRB2)-targeted JTX-8064 plus the anti-PD1 inhibitor JTX-4014 (pimivalimab) in immune-checkpoint inhibitor (ICI) pre-treated patients (pts) with advanced or metastatic renal cell cancer (mRCC): Results from the multi-stage phase 1-2 INNATE trial.

Primo N. Lara Jr., Stew Kroll, Jonathan Alexander Chatzkel, Deanna Gek Koon Teoh, Vincent T Ma, Deepak Kilari, Clara Hwang, Randy F. Sweis, Kiran Yalamanchili, Julio Antonio Peguero, Tianhong Li, Mamta Parikh; University of California, Davis Comprehensive Cancer Center, Sacramento, CA; Jounce Therapeutics, Cambridge, MA; University of Florida Department of Medicine/Division of Hematology/Oncology, Gainesville, FL; University of Minnesota, Minneapolis, MN; University of Wisconsin Carbone Cancer Center, Madison, WI; Department of Medicine, Division of Hematology and Oncology, The Medical College of Wisconsin, Milwaukee, WI; Division of Hematology/Oncology, Department of Internal Medicine, Henry Ford Cancer, Detroit, MI; University of Chicago, Chicago, IL; Joe Arrington Cancer Research and Treatment Center, Lubbock, TX; Oncology Consultants, Houston, TX; UC Davis Comprehensive Cancer Center, Sacramento, CA

Background: Disease progression following treatment of mRCC pts with ICl-based therapy (tx) is nearly universal, warranting evaluation of novel immunotherapeutic approaches. LILRB2 is an immune checkpoint molecule expressed primarily in cells of myeloid origin (e.g., monocytes/macrophages). Inhibition of LILRB2 reprograms macrophages from an immunosuppressive (M2) to an immunostimulatory (M1) phenotype. JTX-8064 is a humanized monoclonal antibody that binds to LILRB2, blocking its interaction with MHC1 molecules. Preclinical studies suggest that JTX-8064 can overcome anti-PD(L)1 resistance mechanisms. Here we report the results of an expansion cohort of previously-treated mRCC pts in INNATE, a multi-stage phase 1-2 trial of JTX-8064 in combination with anti-PD1 agents in solid tumors. **Methods:** Pts with pathologically-confirmed clear cell mRCC progressing on or after anti-PD(L)1 tx in the most recent prior line, acceptable end-organ function, and ECOG PS 0-1 were treated with JTX-8064 700 mg and JTX-4014 500 mg IV q3 weeks. Primary endpoint was overall response rate (ORR); secondary endpoints were safety, disease control rate (DCR), progression-free survival (PFS), & overall survival (OS). A Simon 2-stage design (n=10+19) was employed where ORR >= 20% was deemed to be of further interest versus null hypothesis of ORR <= 5%, with alpha=0.05. **Results:** 31 pts were enrolled, with median age of 64 years (range 38-85); 84% males; 16% Hispanic; 93% White; 45% PS=0; 71% one prior tx line. Of 28 pts evaluable for response, 1 CR, 1 PR, 14 SD (6 SD>= 6 months), and 11 PD were seen for an ORR of 7% & DCR of 54%.Median PFS was 4 months (95%CI: 2, 6.8); 12-month OS was 75% (95%CI: 55,88). Tx-related adverse events (AE) of all grades were reported in 11 pts (45%), most commonly fatigue (16%) & diarrhea (10%). Only 4 protocol-related G3-4 AEs were reported: thrombocytopenia (G4); diplopia, diarrhea, & bradycardia (all G3). Three on-study deaths (hypotension; cardio-respiratory arrest; & unknown) were deemed unrelated to protocol tx. **Conclusions:** While ORR did not meet the protocol-defined efficacy target, evidence of anti tumor activity was seen in ICI pre-treated mRCC pts with combination JTC-8064 + JTX-4014. Treatment was reasonably well-tolerated. Identification & evaluation of clinical and molecular phenotypes most likely to benefit from LILRB2-targeted therapies are warranted. Clinical trial information: NCT04669899. Research Sponsor: None.

4532 Poster Session

Subcutaneous (SC) nivolumab (NIVO) vs intravenous (IV) NIVO in patients with previously treated advanced or metastatic clear cell renal cell carcinoma (ccRCC): Safety and patient-reported outcomes (PROs) of the randomized phase 3 CheckMate 67T trial.

Maria T. Bourlon, Laurence Albiges, Matias Rodrigo Chacon, Hernan Cutuli, Bogdan Zurawski, Jose Mauricio Mota, Ignacio Magri, Mauricio Burotto, Murilo Luz, Juliana Menezes, Eduardo Patricio Yanez Ruiz, Marco Maruzzo, Sergio Bracarda, Subhransu Prusty, Dhanrajsinh Rathod, Zhuoxin Yu, Balmeet Gurm, Matthew Dixon, Saby George; Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, DF, Mexico; Gustave Roussy, Université Paris Saclay, Paris, France; Fundación Cancer - Fuca, Buenos Aires, Argentina; Hospital Sirio Libanes, Buenos Aires, Argentina; The F. Lukaszczyk Oncology Center, Bydogoszcz, Poland; Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Instituto Medico Rio IV, Río Cuarto, Argentina; Centro de Investigación Clínica Bradford Hill, Recoleta, Chile; Erasto Gaertner Hospital, Curitiba, Brazil; Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; Department of Internal Medicine, Hematology-Oncology Unit, University of the Frontera, Temuco, Chile; Istituto Oncologico Veneto, Padua, Italy; Medical and Translational Oncology Unit, Department of Oncology, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy; Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Lawrenceville, NJ; Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: CheckMate 67T (NCT04810078), a multicenter, randomized, open-label, phase 3 study, evaluated pharmacokinetics and objective response rate (ORR) noninferiority of NIVO SC vs IV in previously treated patients with advanced/metastatic ccRCC. Noninferiority endpoints of exposure (time-averaged serum concentration over the first 28 days and trough serum concentration at steady state) and efficacy (ORR by BICR) were met. Safety was comparable in the SC vs IV arms. NIVO-related immunogenicity was as expected for SC administration and further assessments did not identify apparent clinically meaningful impact. This report focuses on additional safety analyses and PROs. **Methods:** Patients were randomized 1:1 to NIVO SC 1200 mg + recombinant human hyaluronidase PH20 Q4W (n = 248) or NIVO IV 3 mg/kg Q2W (n = 247). Eligibility criteria were previously reported. Safety analyses were performed for all-causality adverse events (AEs) across weight categories (< 50 kg, ≥ 50 kg–< 70 kg, ≥ 70–< 90 kg, ≥ 90 kg–< 110 kg, and ≥ 110 kg). The onset, management, and resolution of treatment-related select AEs were studied; duration and grade of local site reactions and the effect of immunogenicity on local site reactions were reported. PROs were assessed using the Functional Assessment of Chronic Illness Therapy (FACIT) GP5 item. **Results:** The overall AE incidence rates in the SC arm were generally comparable to or lower than in the IV arm across weight categories, but limited by small sample sizes in the < 50 kg and ≥ 110 kg subgroups. Across the treatment-related select AE categories, most events were manageable with established algorithms and resolved with immune-modulating medications. Local site reactions were mild to moderate with a median duration of 2.0 and 0.01 days in the SC and the IV arms, respectively; most resolved without treatment. The proportion of patients with a local site reaction of any grade was 8.1% in the SC arm and 2.0% in the IV arm. In patients testing NIVO-specific anti-drug antibody (ADA)-positive, 15.2% of patients in the SC arm reported a local site reaction, but all were grade 1–2 and most resolved without treatment. No hypersensitivity/infusion reaction select AEs were reported in ADA-positive patients in either arm. A majority of patients in SC and IV arms reported minimal bother by treatment side effects in their FACIT GP5 scores. **Conclusions:** The safety profile of SC was consistent with IV, supporting the use of NIVO SC as an option improving patient experience. This aligns with patient preference for SC administration over IV. Analyses based on weight and ADA subgroups were consistent with the known NIVO safety profile. Toxicity was manageable with immune-modulating medications. FACIT GP5 scores indicated no bother by treatment side effects. Clinical trial information: NCT04810078. Research Sponsor: Bristol Myers Squibb.

Matched tissue and circulating tumor DNA (ctDNA) analysis in renal cell carcinoma (RCC): Results from a multimodal real-world database.

Rana R. McKay, Chinmay Jani, Eli Tran, Adam J Hockenberry, Ellen B. Jaeger, Nabil Husni, Melissa Conrad Stoppler, Jacob Mercer, Sumanta Kumar Pal, Neeraj Agarwal, Toni K. CHOUEIRI, Brent S. Rose, Aditya Bagrodia; University of California, San Diego Health, La Jolla, CA; University of Miami Sylvester Comprehensive Cancer Center/ Jackson Health System, Miami, FL; School of Medicine, University of California, San Diego, La Jolla, CA; Tempus AI, Chicago, IL; Tempus Labs, Chicago, IL; City of Hope Comprehensive Cancer Center, Duarte, CA; Huntsman Cancer Institute, Salt Lake City, UT; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; University of California, San Diego, San Diego, CA

Background: Next generation sequencing (NGS) of ctDNA can complement tissue NGS and is a non-invasive test that can be conducted serially, with the potential to enhance assessment of spatial and temporal molecular tumor heterogeneity. Here, we investigated mutations in RCC patients from ctDNA and matched tissue genomic profiling. **Methods:** From the Tempus multimodal database, we retrospectively analyzed de-identified NGS data from patients (pts) with RCC that had dual tissue (Tempus xT, 648 genes) and ctDNA testing (Tempus xF, 105 genes). Pts with matched samples (collected +/- 90 days of one another) were included. Clinical characteristics and select pathogenic somatic short variants (PSSV) and copy number variants [(amplifications and deletions, two copy number losses (CNL)] were evaluated. Concordance analyses were restricted to the 105 genes tested on the ctDNA panel and further restricted to short variants, with the exception of amplifications and CNL detected by both xF and xT. **Results:** Among all pts (n=393), the median age was 61 years and 71% were male. Median time from tissue to blood collection was 21 days (IQR, 7, 39). 67% (n=265) and 68% (n=266) had metastatic disease at the time of tissue and blood collection, respectively. The most common tissue sites were kidney (49%, n=189), bone (11%, n=43), lung (9%, n=34), lymph node (8%, n=29), liver (6%, n=23), and brain/CNS (4%, n=17). Genes harboring the most common PSSV in tissue included *VHL* (59% n=232), *PBRM1* (31%, n=123), *SETD2* (23%, n=91), and *TP53* (14%, n=54). Genes with common PSSV in ctDNA included *TP53* (23%, n=91), *VHL* (18%, n=69), *BAP1* (6%, n=23), and *PBRM1* (5%, n=21). The combination of tissue and ctDNA testing increased detection of mutations (Table). There was higher concordance between somatic alterations in select genes among patients with metastases. **Conclusions:** This analysis shows that ctDNA profiling is complementary to tissue based NGS in RCC and can increase the detection of mutations. Concordance between ctDNA and tissue profiling increased in individuals with metastatic disease. Future research is warranted to understand how longitudinal ctDNA analysis can define biomarkers of response and resistance at the mutation and ctDNA fraction levels.
Research Sponsor: None.

Gene	+xT &/or xF All Pts	+xT Only All Pts	+xF Only All Pts	+xT & xF +xT &/or xF	+xT & xF +xT &/or xF (Metastatic)	+xT & xF +xT &/or xF (Non-Metastatic)
VHL	237 (60%)	168 (43%)	5 (1%)	64/237 (27%)	51/158 (32%)	9/72 (13%)
PBRM1	123 (31%)	102 (26%)	0 (0%)	21/123 (17%)	15/88 (17%)	4/30 (13%)
TP53	112 (28%)	21 (5%)	58 (15%)	33/112 (29%)	28/76 (37%)	3/33 (9%)
TERT	49 (12%)	38 (10%)	4 (1%)	7/49 (14%)	6/36 (17%)	1/11 (9%)
BAP1	47 (12%)	24 (6%)	1 (<1%)	22/47 (47%)	19/34 (56%)	1/11 (9%)
ARID1A	23 (6%)	12 (3%)	4 (1%)	7/23 (30%)	5/20 (25%)	1/6 (17%)
BRCA2	16 (4%)	12 (3%)	3 (1%)	1/16 (6%)	1/12 (8%)	0/3 (0%)
TSC1	14 (4%)	9 (2%)	0 (0%)	5/14 (36%)	3/9 (33%)	1/3 (33%)
MTOR	10 (3%)	8 (2%)	0 (0%)	2/10 (20%)	1/7 (14%)	0/2 (0%)

Belzutifan in patients with advanced clear cell renal cellcarcinoma (ccRCC): Subgroup analysis of the phase 2 LITESPARK-013 study.

Michael B. Atkins, Pooja Ghatalia, Jaime R. Merchan, Saby George, John Haanen, Howard Gurney, Rahul Ravilla, Astrid Aplonia Maria Van Der Veldt, Benoit Beuselinck, Ilya Pokataev, Britt Suelmann, Mark H. Tuthill, Daniel A. Vaena, Flora Zagouri, Jianxin Lin, Rodolfo F. Perini, Yanfang Liu, James Brugarolas, Neeraj Agarwal; Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; Fox Chase Cancer Center, Philadelphia, PA; University of Miami Hospital and Clinics, Sylvester Comprehensive Cancer Center, Cancer Research Services, Miami, FL; Roswell Park Cancer Institute, Buffalo, NY; Netherlands Cancer Institute, Amsterdam, Netherlands; MQ Health, Macquarie University, Sydney, NSW, Australia; New York Oncology Hematology, Albany, NY; Erasmus MC, Rotterdam, Netherlands; UZ Leuven, Leuven, Belgium; Moscow City Clinical Oncology Hospital No. 1, Moscow, Russian Federation; University Medical Center Utrecht, Utrecht, Netherlands; Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; West Cancer Center and Research Institute, Memphis, TN; Alexandra General Hospital, Athens, Greece; Merck & Co., Inc., Rahway, NJ; UT Southwestern Medical Center, Dallas, TX; Huntsman Cancer Institute, Salt Lake City, UT

Background: In the randomized phase 2 LITESPARK-013 study (NCT04489771), the first-in-class HIF-2α inhibitor belzutifan showed comparable antitumor activity in patients with pretreated advanced ccRCC at 200 mg and 120 mg doses (objective response rate [ORR]: 23.1% vs 23.7%; 1-sided *P*= 0.5312). We present results of a post hoc analysis of the pooled population (200 mg and 120 mg arms) across patient subgroups based on prior therapy and IMDC risk group. **Methods:** Patients with advanced ccRCC, measurable disease per RECIST v1.1, a Karnofsky Performance Scale score of ≥70%, ≤3 prior systemic regimens for advanced ccRCC (including an anti–PD-(L)1 regimen), and disease progression during or after an anti–PD-(L)1 regimen were randomly assigned 1:1 to receive belzutifan 200 mg or 120 mg QD. End points in the pooled population and subgroups were ORR and duration of response per RECIST v1.1 by blinded independent central review. Data cutoff was February 10, 2023. **Results:** A total of 154 patients were enrolled (200 mg, n = 78; 120 mg, n = 76). In the pooled population, the median age was 64.0 years, 127 patients (82.5%) had intermediate/poor risk per IMDC criteria, 110 patients (71.4%) received 1-3 prior tyrosine kinase inhibitor (TKI) regimens, and 81 patients (52.6%) received 2 or 3 prior lines of therapy. As of the data cutoff date, 39 patients (25.3%) in the pooled population remained on treatment. Median follow-up was 20.1 months (range, 14.8-28.4). In the pooled population, ORR was 23.4% (95% CI, 16.9-30.9; 4 complete responses [CRs], 32 partial responses [PRs]) and median duration of response (DOR) was 16.1 months (range, 2.1+ to 23.5+). Additional efficacy analyses for subgroups are presented in the table. **Conclusions:** This post hoc analysis from the LITESPARK-013 study of patients with pretreated advanced ccRCC suggests that belzutifan has antitumor activity regardless of prior lines of therapies and prognostic risk category. These results further support belzutifan as a treatment option for advanced RCC. Clinical trial information: NCT04489771. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	ORR, % (95% CI)	DOR, Months (range)
1 prior line of therapy n = 73	28.8% (18.8-40.6); 3 CRs, 18 PRs	16.1 (2.6+ to 18.4+)
2 or 3 prior lines of therapy n = 81	18.5% (10.8-28.7); 1 CR, 14 PRs	10.2 (2.1+ to 23.5+).
Prior anti–PD-(L)1 regimens only n = 44	34.1% (20.5-49.9); 3 CRs, 12 PRs	Not reached (3.7 to 23.5+)
Both prior anti–PD-(L)1 and TKI regimens n = 110	19.1% (12.2-27.7); 1 CR, 20 PRs	16.1 (2.1+ to 18.4+).
Received TKI regimens containing cabozantinib or lenvatinib n = 40	20.0% (9.1-35.6); 0 CRs, 8 PRs	8.4 (2.1+ to 16.1+)
Received other TKI regimens n = 70	18.6% (10.3-29.7); 1 CR, 12 PRs	16.1 (2.6+ to 18.4+).
Favorable IMDC risk n = 27	29.6% (13.8-50.2); 0 CRs, 8 PRs	Not reached (2.9 to 15.2+)
Intermediate/poor IMDC risk n = 127	22.0% (15.2-30.3); 4 CR, 24 PRs	16.1 (2.1+ to 23.5+)

4535 Poster Session

Health-related quality of life (HRQoL) with nivolumab (NIVO) subcutaneous (SC) or intravenous (IV) in patients (pts) with advanced or metastatic clear cell renal cell carcinoma (ccRCC) who have received prior therapy in the phase 3 CheckMate 67T trial.

Saby George, Maria T. Bourlon, Matthew Dixon, Jennifer Lord-Bessen, Gill Worthy, Katie Frampton, Christine Yip, Rachael Lawrance, Fiona Taylor, Laurence Albiges; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Bristol Myers Squibb, Lawrenceville, NJ; Adelphi Mill, Bollington, Cheshire, United Kingdom; Adelphi Values, Boston, MA; Institut Gustave Roussy, Villejuif, France

Background: NIVO IV has improved outcomes in multiple tumor types. Evolving treatment paradigms have created a need for administration options that address treatment burden and improve efficiencies of healthcare systems. In a phase 1/2 study (CheckMate 8KX), pts were highly satisfied with NIVO SC and preferred it over NIVO IV [Lonardi et al, ESMO 2022; Lonardi et al, SITC 2023]. CheckMate 67T (NCT04810078) is a multicenter, randomized, open-label, phase 3 study that demonstrated pharmacokinetic and objective response rate noninferiority of NIVO SC vs IV in pts with locally advanced or metastatic ccRCC [George et al, ASCO-GU 2024]. This exploratory analysis assessed non-inferiority of HRQoL between pts randomized to NIVO SC (n=248) vs NIVO IV (n=247) in CheckMate 67T. **Methods:** HRQoL was measured using patient-reported outcomes (PROs), FKSI-19 (kidney cancer-related HRQoL) and the EQ-5D-5L (pt's health status). FKSI-19 total score (range 0-76, higher score better HRQoL)and EQ-5D-5L visual analogue scale (VAS) (range 0-100, higher score better health HRQoL) scores were evaluated longitudinally on-treatment visits with ≥10 pts per arm included in model [week 57]) using linear mixed models (constrained longitudinal data analysis), with least squares (LS) mean changes from baseline and differences in the LS mean between NIVO SC and NIVO IV assessed; non-inferiority of NIVO SC vs NIVO IV was evaluated by examining overall treatment differences for on-treatment visits relative to prespecified thresholds. **Results:** PRO data were available for 247 pts (99.6%) for NIVO SC and 245 pts (99.2%) for NIVO IV, with completion rates >87% across instruments up to week 57 for both treatment arms. HRQoL was maintained over time for both NIVO arms for FKSI-19 total score and subscales and EQ-5D-5L VAS. NIVO SC was non-inferior to NIVO IV across FKSI-19 total score and subscales and EQ-5D-5L VAS (Table). **Conclusions:** These results demonstrate maintenance of HRQoL for pts with advanced or metastatic ccRCC while on treatment with NIVO, regardless of the mode of administration (SC or IV), supporting the use of NIVO SC as a new option to align with patient preferences. Clinical trial information: NCT04810078. Research Sponsor: Bristol Myers Squibb.

PRO	Overall LS Mean Change From Baseline (95% CI)		Overall LS Mean Difference (95% CI) (NIVO SC – NIVO IV)	Non-Inferiority Threshold*
	NIVO SC	NIVO IV		
FKSI-19 total score	0.2 (-0.6, 0.9)	0.6 (-0.1, 1.4)	-0.5 (-1.4, 0.5)	> -5 points
EQ-5D-5L VAS	3.0 (1.5, 4.4)	3.2 (1.8, 4.6)	-0.2 (-1.9, 1.4)	> -7 points

*non-inferiority thresholds are negative, relating to worsening of PRO outcomes CI = confidence interval.

Intratumoral T-cell infiltration and response to nivolumab plus ipilimumab in patients with metastatic clear cell renal cell carcinoma from the CheckMate-214 trial.

Sayed Matar, Opeyemi Jegede, Thomas Denize, Fatme Ghandour, Yasmin Nabil Laimon, Nourhan El Ahmar, Aseman Bagheri Sheshdeh, Varunika Savla, Razan Assaad Mohanna, Paul J. Catalano, David A. Braun, Maxine Sun, Saurabh Gupta, Sai Vikram Vemula, Gordon J. Freeman, Robert J. Motzer, Michael B. Atkins, David F. McDermott, Toni K. CHOUEIRI, Sabina Signoretti; Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; Yale Cancer Center, Yale School of Medicine, New Haven, CT; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Bristol Myers Squibb, Princeton, NJ; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC; Beth Israel Deaconess Medical Center, Boston, MA

Background: We have previously shown that levels of antigen-experienced but not terminally exhausted $CD8^+$ TILs (i.e. $CD8^+PD1^+TIM3^-LAG3^-$ TILs) are associated with improved clinical outcomes in patients (pts) with metastatic clear cell RCC (mccRCC) treated with nivolumab monotherapy within three independent clinical trials (CheckMate-010, CheckMate-025, HCRN GU16-260). Here, we aimed to evaluate the performance of this biomarker in patients with mccRCC treated with nivolumab plus ipilimumab (Nivo+Ipi) versus sunitinib (Sun) as part of the CheckMate-214 (CM-214) clinical trial. **Methods:** Pre-treatment, formalin fixed paraffin embedded (FFPE) tumor samples from the CM-214 clinical trial were stained with a multiplex immunofluorescence (mIF) assay and the density of CD8+PD1+TIM3-LAG3- TILs (mIF biomarker) was quantified using Halo image analysis software. The correlation between the mIF biomarker and clinical outcomes, including progression-free survival (PFS), and objective response rate (ORR), was evaluated using Cox proportional hazards and logistic regression models. The significance level was set at 5% (2-sided). **Results:** Following quality control, mIF data were obtained for 255 intermediate-and poor-risk patients (Nivo+Ipi= 136, Sun= 119). A comparison between patients with mIF biomarker data available and those without, showed no imbalance with regards to ORR and PFS in the Nivo+Ipi group. However, in the Sun group, pts with mIF biomarker data showed a higher ORR compared to pts without available data (33% vs 24%). In Nivo+Ipi-treated pts, the mIF biomarker measured as continuous variable showed a trend for a positive association with ORR (OR = 1.23, p = 0.1162) but no association with PFS (HR 0.97, p = 0.688). In Sun-treated pts, the mIF biomarker measured as continuous variable showed a trend for a positive association with ORR (OR = 1.32, p = 0.0726) and a significant positive association with PFS (HR= 0.78, p = 0.004. However, given that Sun-treated pts with available mIF data were enriched for responders, results obtained in the Sun group should be interpreted with caution. **Conclusions:** In contrast to Nivo monotherapy, pre-treatment levels of CD8+ PD1+ TIM-3-LAG-3- TILs were not associated with improved clinical outcomes to Nivo+Ipi. These results suggest that the baseline levels of intratumoral T-cell inflammation do not represent a strong determinant of response to anti-CTLA4-based therapy in mccRCC, which is consistent with the knowledge that anti-CTLA4 therapy (Ipi) can recruit new T cells into the tumor. The association between CD8+ PD1+ TIM-3-LAG-3- TILs and outcomes on sunitinib needs further investigation. Research Sponsor: National Cancer Institute; R01 1R01CA266424-01A1; National Cancer Institute; P50-CA101942-19.

Belzutifan plus lenvatinib (len) for Chinese patients (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC): Preliminary results of cohort 1 of the phase 1 LITESPARK-010 study.

Xinan Sheng, Hongqian Guo, Xin Yao, Fangjian Zhou, Jimin Chen, Shun Zhang, Juan Li, Lei Diao, Pei Dong, Xiaoqing Li, Zhewei Zhang, Anne Chain, Pengfei Zhu, Weijuan Zhang, Ding Wang, Jun Guo; Peking University Cancer Hospital and Institute, Beijing, China; Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Sun Yat-Sen University Cancer Center, Guangzhou, China; The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China; Merck & Co., Inc., Rahway, NJ; MSD (China) Co., Ltd., Shanghai, China

Background: Belzutifan, a first-in-class HIF-2α inhibitor, alone or in combination with a VEGFR-TKI, has shown durable antitumor activity in first- and subsequent-line settings of advanced ccRCC. LITESPARK-010 (NCT05030506) is a phase 1, 2-cohort, open-label study of belzutifan + len, with or without pembrolizumab, in Chinese pts with advanced ccRCC. We present preliminary results cohort 1. **Methods:** Chinese adults with histologically confirmed ccRCC who had 1-3 prior treatment regimens received belzutifan 120 mg PO QD for 3 wk followed by belzutifan 120 mg + len 20 mg PO QD until intolerable toxicity, disease progression, or pt withdrawal. The study included a dose-limiting toxicity (DLT) phase of 21 days after the start of combination treatment. Dual primary end points were safety and PK. Secondary end points included ORR, DOR, and PFS per RECIST v1.1 by investigator assessment and OS. **Results:** As of August 29, 2023, 24 pts were enrolled in cohort 1 and 23 received combination treatment; 1 pt discontinued in the monotherapy period because of treatment with non-study anti-cancer therapy. Median age was 61 years, 17 pts (71%) were male, and 14 (58%) had intermediate/poor IMDC risk. 14 pts (58%) received 1 prior line of therapy and 10 (42%) received ≥2 prior lines. Five pts (21%) received prior therapy with a PD-(L)1 inhibitor. As of the data cutoff date, 11 pts (46%) remained on treatment. Median follow up was 14.4 mo (range, 1.6-22.1). Ten pts were evaluated in the DLT phase, and 1 experienced a DLT (grade 2 treatment-related transient ischemic attack). All 24 pts (100%) experienced a treatment-related AE (TRAE) of any grade, most commonly anemia (100%) and proteinuria (88%). Grade 3 or 4 TRAEs occurred in 17 pts (71%), most commonly anemia (29%) and hypertension (29%). One pt (4%) experienced grade 3 hypoxia. No pts died (grade 5) due to a TRAE. After a single dose of belzutifan monotherapy, median T_{max} was 1.8 h (range, 0.6-8.0), geometric mean AUC_{0-24} was 22,400 h·ng/mL (90% CI, 19,600-25,500), and geometric mean C_{max} was 1640 ng/mL (90% CI, 1490-1820). Steady-state concentration was reached after 14 days of belzutifan monotherapy treatment; the accumulation ratio of AUC_{0-24} was 1.7 (90% CI, 1.5-1.9). Belzutifan + len treatment had similar PK to belzutifan monotherapy. In all 24 pts, confirmed ORR was 50% (95% CI, 29-71; all PRs). Median DOR was not reached (NR; range, 3.5-20.4+ months); 50% of responders remained in response for ≥12 mo per Kaplan-Meir estimate. Median PFS was 13.7 mo (95% CI, 8-NR) and median OS was NR (95% CI, NR-NR). The 12-mo PFS and OS rates were 57% and 75%, respectively. **Conclusions:** Preliminary data from the belzutifan + len showed promising antitumor activity in Chinese pts with previously treated ccRCC. The safety of belzutifan 120 mg + len 20 mg was consistent with the safety profiles of the individual drugs. Clinical trial information: NCT05030506. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Eisai Inc., Nutley, NJ.

Efficacy of post-lenvatinib treatments in patients (pts) with advanced renal cell carcinoma (aRCC).

Justine Panian, Caiwei Zhong, Sharon Choi, Roxanne Quinn, Evan Ferrier, Eddy Saad, Renee Maria Saliby, Carmel Malvar, Sumanta Kumar Pal, Hedyeh Ebrahimi, Ben Tran, Andrew James Weickhardt, Aly-Khan A. Lalani, Cristina Suárez, Guillermo de Velasco, Ravindran Kanesvaran, Martin Zarba, Toni K. CHOUEIRI, Daniel Yick Chin Heng, Rana R. McKay; University of California, San Diego, San Diego, CA; Dana-Farber Cancer Institute, Boston, MA; University of California, San Diego, La Jolla, CA; Tom Baker Cancer Centre, Calgary, AB, Canada; City of Hope Comprehensive Cancer Center, Duarte, CA; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Austin Hospital, Heidelberg, Australia; McMaster University, Hamilton, ON, Canada; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Medical Oncology Department, Hospital Universitario 12 De Octubre, Madrid, Spain; Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; Alexander Fleming Institute, Buenos Aires, Argentina; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; University of California, San Diego Health, La Jolla, CA

Background: Lenvatinib is a tyrosine kinase inhibitor (TKI) that targets both vascular endothelial growth factor (VEGF) receptor and fibroblast growth factor receptor. It has demonstrated efficacy both in the upfront and refractory disease settings. However, there is a lack of data surrounding the efficacy of TKIs post-lenvatinib exposure. In this study, we investigate the activity of post-lenvatinib therapies in pts with aRCC. **Methods:** We conducted a retrospective analysis utilizing the International Metastatic Database Consortium (IMDC). Pts having received treatment post lenvatinib exposure were eligible and divided into two cohort: pts post-1st line lenvatinib (2nd line cohort) and pts post-2nd line lenvatinib (3rd line cohort). The primary objective was objective response rate (ORR) and time to treatment failure (TTF). ORR was summarized with 95% two-sided exact binomial confidence interval. TTF was defined as time from treatment initiation to drug cessation for any reason censored at the date of last follow-up. **Results:** Overall, 84 pts received 1st line lenvatinib of whom 43 (51%) remain on therapy, 20 (24%) received 2nd line treatment, and 21 (25%) received no subsequent treatment. All pts received 1st line pembrolizumab + lenvatinib (ORR 50%, median TTF 9.7 months). Reason for lenvatinib discontinuation was progression (50%), progression + toxicity (20%), toxicity (15%), or other (15%). For the 2nd line cohort, median age was 61 years, most pts were male (85%), had prior nephrectomy (75%), clear cell histology (85%), and were IMDC intermediate/poor risk (55%). 2nd line therapy regimens included TKI monotherapy (80%), TKI-IO (5%), and other (15%). The ORR to 2nd line treatment was 5% (95% CI 0.2-25) and median TTF was 5.8 months (95% CI 1.9-14.9). Of 2nd line lenvatinib-exposed pts (n=84), 24 (29%) remain on treatment, 34 (40%) received 3rd line treatment, and 26 (31%) did not receive additional therapy. Most pts received 2nd line everolimus + lenvatinib (97%) (ORR 39%, median TTF 5.9 months). Reason for lenvatinib discontinuation was progression (59%), progression + toxicity (9%), toxicity (12%), or other (21%). For the 3rd line cohort, median age was 67 years, most pts were male (68%), had prior nephrectomy (88%), clear cell histology (68%), and were IMDC intermediate/poor risk (77%). 3rd line treatments included TKI alone (50%), IO-TKI (38%), and other (12%). The ORR to 3rd line treatment was 12% (95% CI 3.3-27) and median TTF was 2.8 months (95% CI 1.9-7.4). **Conclusions:** In this analysis, we demonstrate modest activity of TKI-based therapy post-lenvatinib exposure. Our study highlights the need for improved treatment options for pts progressing on lenvatinib-based therapies. Research Sponsor: None.

Camrelizumab plus apatinib for advanced renal cell carcinoma patients after first-line tyrosine kinase inhibitor treatment failure: A multicenter phase II trial.

Lijuan Jiang, Xia Zheng, Wensu Wei, Yulu Peng, Deling Wang, Zhiling Zhang, Shengjie Guo, Hui Han, Xiuyu Cai, Fangjian Zhou, Pei Dong; Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Medical Imaging, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Urology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Department of Urology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of General Internal Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Previous studies have demonstrated the benefit of combining immunotherapy with antiangiogenic agents in patients with advanced renal cell carcinoma (aRCC). The efficacy of apatinib, a vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor (TKI), has been documented in aRCC. In contrast, the efficacy of camrelizumab, a PD-1 inhibitor, has not been reported in RCC, although its efficacy and safety have been established in various cancer types. This study aims to evaluate the efficacy and safety of camrelizumab plus apatinib in aRCC following the failure of first-line TKI therapy. **Methods:** This multicenter, single-arm, phase II trial enrolled patients with aRCC who had failed first-line TKI treatment. Patients received 200 mg of camrelizumab intravenously every two weeks and 250 mg of apatinib orally once daily until disease progression or unacceptable toxicity occurred, with camrelizumab treatment lasting up to two years. The primary endpoint was progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors version 1.1. **Results:** Between August 2020 and January 2024, 35 patients were enrolled in the study and received treatment. The median age was 57 years (range: 39-81), with 31 (88.6%) being male. A total of 27 (77.1%) patients presented with lung metastases. As of the cut-off date, January 8, 2024, the median follow-up duration was 16.5 months (range: 0-33). Of these patients, 12 (34.3%) achieved a partial response, and 17 (48.6%) maintained stable disease, resulting in an objective response rate of 34.3% (95% confidence interval [CI], 19.1-52.2) and a disease control rate of 82.9% (95% CI, 66.4-93.4). Two out of five patients with progressive disease (PD) benefited from continued treatment with camrelizumab plus apatinib for more than 4 months after the first PD. The median PFS was 10.0 months (95% CI, 6.1-14.9), and the median overall survival was 28.4 months (95% CI, 19.7-not reached). Of all patients, 27 (77.1%) experienced treatment-related adverse events of grade 3 or higher, with the most common being proteinuria (25.7%), hypertension (20.0%), and alanine aminotransferase increased (14.3%) and aspartate aminotransferase increased (14.3%). **Conclusions:** The combination of camrelizumab and apatinib demonstrates encouraging antitumor activity and a favorable safety profile as a second-line treatment option for patients with aRCC. Clinical trial information: ChiCTR2000034384. Research Sponsor: None.

Efficacy endpoints.

Endpoints	All (n=35)
Best overall response, n (%)	
Partial response	12 (34.3)
Stable disease	17 (48.6)
Progressive disease	5 (14.3)
Not available	1 (2.9)
Objective response rate, %, 95%CI	34.3 (19.1, 52.2)
Disease control rate, %, 95%CI	82.9 (66.4, 93.4)
Progression-free survival, months, median, 95%CI	10.0 (6.1-14.9)
Overall survival, months, median, 95%CI	28.4 (19.7-NR)

Preliminary results from a phase II clinical study of first-line drugs combined with stereotactic body radiotherapy (SBRT) in the treatment of oligoprogressive renal cell carcinoma.

Xinyue Zhang, Ruiqi Liu, Yang Liu, Zhiling Zhang, Jianming Gao, Shengjie Guo, Hui Han, Fangjian Zhou, Pei Dong, Liru He; Department of Radiation Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Urology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: For metastatic renal cell carcinoma (mRCC) patients (pts) with oligoprogression, escalation of systemic therapy (STE) to the next line of treatment is one of the major strategies but not the only option. Our study aimed to investigate the safety and efficacy of stereotactic body radiotherapy (SBRT) to mRCC pts with oligoprogression after first-line systemic therapy. **Methods:** This is a single-arm, phase II study enrolling oligoprogressive mRCC pts, defined as ≤ 3 progressive lesions with total metastases ≤ 5, who have received first-line systemic therapy for more than three months (ChiCTR2000032947). No liver or brain metastasis was allowed. Nephrotic focus was treated before or after enrollment. Pts remained on current first-line systemic therapy and received SBRT for all the oligoprogressive lesions, with 35-45Gy in 5 fractions. If oligoprogressive lesions appeared > 6 months after the end of SBRT, which were not irradiated, a second round of SBRT could be allowed. Primary endpoint was progression-free survival (PFS); secondary endpoints were local control (LC) rate, time to STE, overall survival (OS) and safety. **Results:** From June 2020 to Jan 2024, 30 pts were enrolled, and 27 pts (median age: 55 years; male-to-female ratio: 16:11) were evaluable for efficacy after SBRT. Most pts (74.1%) had a clear cell histology, and most pts (92.6%) were at an intermediate or a poor risk according to the International Metastatic RCC Database Consortium criteria. Sixteen pts had one progressive lesion and 11 pts had 2-3 lesions. The median time to oligoprogressive disease under first-line systemic therapy (mostly TKI monotherapy: 85.2%) was 13.6 months. The most common sites for SBRT were bone (32.4%), lymph node (23.5%) and lung (23.5%). At a median follow-up of 23.5 months, the LC rate was 97.1%. Six-month PFS, 12-month PFS, 18-month PFS, 24-month PFS and median PFS were 88.9%, 54.2%, 36.4%, 22.7% and 15.0 months, respectively. The 24-month OS and median OS were 78.5% and not reached. Grade 3-4 treatment-related adverse events (AEs) occurred in 44.4% pts, and the most common AEs were hematological toxicity (18.5%), hypertension (18.5%), and palmar-plantar erythrodysesthesia syndrome (7.4%). No SBRT-related grade 3-4 toxicity was observed. **Conclusions:** SBRT is a safe and an effective treatment for oligoprogressive mRCC, with a notable extension of the ongoing first-line systemic therapy. Clinical trial information: ChiCTR2000032947. Research Sponsor: None.

A phase I/II study of talazoparib and axitinib in patients with advanced clear cell renal cell carcinoma.

Ritesh R. Kotecha, Sahil D Doshi, Andrea Knezevic, Rachel Jacobi, David H Aggen, Deaglan Joseph McHugh, Neil J. Shah, Marie Isabel Carlo, Niamh M. Keegan, Yogini Gayadin, Joshua Chaim, Darren R. Feldman, Robert J. Motzer, Martin H Voss; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Targeting the VEGF pathway is a backbone therapeutic for patients with advanced clear cell renal cell carcinoma (ccRCC). Tumor and tissue hypoxia may also lead to DNA repair suppression and PARPs are key regulators of DNA damage and genomic maintenance which interact with HIF proteins. Pairing a potent VEGFR TKI with a selective PARP inhibitor (PARPi) may lead to improved outcomes in ccRCC patients. **Methods:** This was a phase I/II, investigator-initiated, single-center, open-label study (NCT04337970) of talazoparib plus axitinib in previously treated ccRCC patients. In the phase Ib dose escalation, patients must have been previously treated with a PD-1/PD-L1 inhibitor with no maximum lines of prior therapy, and those in dose expansion were required to have prior treatment with a PD-1/PD-L1 inhibitor and prior VEGFR TKI, with a maximum of 2 prior lines of therapy. Patients received escalating doses of talazoparib (0.5 mg, 0.75 mg and 1 mg daily) with axitinib (5 mg twice daily) in a 3+3 design, with primary endpoint of safety and tolerability. After establishing the recommended phase II dose (RP2D), a dose expansion cohort enrolled patients in a Simon two-stage design with a primary endpoint of objective response (ORR), and secondary endpoints including progression-free survival (PFS). **Results:** From 2020-2023, 23 ccRCC patients were enrolled and treated on study. In the dose escalation, 15 patients enrolled across all 3 dose levels and there were 2 observed DLTS (1 in dose levels 2 and 3). Both DLTs was due to a lack of minimum exposure to study drugs during cycle 1 due to treatment-related toxicities. The maximum tolerated dose and RP2D established was 1 mg talazoparib daily with axitinib 5 mg twice daily. In the phase II dose expansion portion, an additional 9 patients were enrolled to evaluate preliminary efficacy. In total, 13/14 patients treated at the RP2D discontinued therapy due to progressive disease. The objective response rate (ORR) was 7% (90% CI 0, 30), with 1 patient achieving a partial response and 12 patients achieving stable disease (86%). With a median follow-up of 13.2 months (R: 6.6 -29), the median PFS was 6.1 months (95% CI 3.5, 8.4) and median overall survival (OS) was 27 months (95% CI 12- NE). Across the study, 13 (56%) patients had at least one treatment-emergent AE of grade 3+, and 9 (39%) patients had at least one treatment-related AE of grade 3+. Most common grade 3+ AEs included diarrhea, nausea, and anemia. **Conclusions:** This is the first clinical study evaluating combination PARPi and VEGFR TKI in metastatic ccRCC patients. This study established the RP2D and MTD of combination talazoparib and axitinib and demonstrated a tolerable safety profile across all dose escalation cohorts. The study did not meet the pre-defined efficacy threshold for further enrollment per Simon stage two design. Exploratory efforts to evaluate this treatment approach with tissue biomarker data remain ongoing. Clinical trial information: NCT04337970. Research Sponsor: Pfizer; 51755433.

A phase II trial of sitravatinib plus nivolumab after progression on prior immune checkpoint inhibitor (ICI) in patients with metastatic clear cell renal cell carcinoma (ccRCC).

Nazli Dizman, Nabil Adra, Ulka N. Vaishampayan, Lianchun Xiao, Ying Yuan, Matthew T Campbell, Jianjun Gao, Amado J. Zurita, Eric Jonasch, Nizar M. Tannir, Amishi Yogesh Shah, Pavlos Msaouel, Andrew Warren Hahn; The University of Texas MD Anderson Cancer Center, Houston, TX; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Sitravatinib, an oral multi-kinase inhibitor targeting VEGFR, TAM, and MET, has been shown to resensitize the tumor microenvironment to ICI by reducing immune-suppressive myeloid cells in metastatic ccRCC (Msaouel, *Sci Transl Med* 2022). ICI is the standard first-line (1L) treatment of metastatic ccRCC, and there is unmet need for improved treatment outcomes after progression on ICI. We hypothesized that sitravatinib plus nivolumab would revert an immunosuppressive tumor microenvironment (TME) to improve objective response rate (ORR) and survival in patients with metastatic ccRCC whose disease progressed on or after ICI. **Methods:** In this investigator-initiated, phase II, multicenter trial (NCT04904302), patients with progressive metastatic ccRCC after 1-2 lines of treatment were enrolled into three cohorts: Cohort A) progression on 1L nivolumab + ipilimumab, Cohort B) progression on 1L pembrolizumab + axitinib or 2L anti-PD-1 therapy after receiving 1L VEGF-targeted monotherapy, Cohort C) progression on 1L or 2L cabozantinib or lenvatinib +/- everolimus either before, after, or in combination with anti-PD-1 ICI. Starting dose of sitravatinib was 100 mg PO daily and nivolumab was 480 mg IV every 4 weeks. The co-primary endpoints were ORR [complete response (CR) + partial response (PR)] and disease control rate [DCR; CR, PR or stable disease (SD) at 24 weeks]. The study was designed to enroll 88 patients with an interim analysis for futility in each cohort using a BOP2 design, but it was terminated early due to discontinuation of sitravatinib development by the sponsor. **Results:** 14 patients were enrolled with 2 in cohort A, 6 in cohort B and 6 in cohort C. Most patients had IMDC intermediate risk disease (n=11, 78.6%), 7 patients had prior nephrectomy (50%), and sarcomatoid dedifferentiation was present in the tumors of 2 patients (7.1%). Across all cohorts, the ORR was 15.4% (2/13, 1 patient not evaluable) and DCR at 24 weeks was 35.7% (5/14). The 2 patients who experienced a PR were pre-treated with nivolumab + ipilimumab and pembrolizumab + axitinib. DCR at 24 months was 63% for Cohort A+B and 0% for Cohort C. After a median follow up of 11.9 months (mo), 10 patients had discontinued treatment (71.4%), all due to disease progression, and 6 patients had died (42.9%). Median progression free survival was 5.5 mo [95% CI 3.8 – not reached (NR)], and median overall survival was 13.3 mo (95% CI 8.77 – NR). Six patients (42.9%) experienced a grade 3-4 adverse event (AE) and 2 patients (14.3%) experienced an immune-mediated AE. **Conclusions:** In this small phase 2 trial with limited sample size due to early termination, sitravatinib plus nivolumab demonstrated a manageable safety profile and produced modest clinical benefit. The observed responses occurred in patients who did not receive prior treatment with cabozantinib or lenvatinib. Clinical trial information: NCT04904302. Research Sponsor: Mirati Therapeutics.

Expression of the receptor tyrosine kinase AXL and clinical outcomes to cabozantinib and everolimus in patients with metastatic renal cell carcinoma enrolled in the METEOR trial.

Yasmin Nabil Laimon, Morgan Paul, Fatme Ghandour, Nourhan El Ahmar, Sayed Matar, Thomas Denize, Aseman Bagheri Sheshdeh, Varunika Savla, Razan Assaad Mohanna, Maxine Sun, Renee Maria Saliby, Eddy Saad, Marc Machaalani, David A. Braun, Dana T. Aftab, Wanling Xie, Toni K. CHOUEIRI, Sabina Signoretti; Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; DFCI/PCC Fellowship Program - Attendings, Boston, MA; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Exelixis, Inc., South San Francisco, CA; Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Harvard Medical School, Boston, MA

Background: High expression of the receptor tyrosine kinase AXL has been associated with resistance to targeted agents and anti-PD-1 therapy in multiple tumor types, including metastatic clear cell Renal Cell Carcinoma (mccRCC). Cabozantinib (cabo), a multitargeted tyrosine kinase inhibitor (TKI) active against VEGFR, MET, and AXL, is approved for the treatment of mccRCC, but no predictive biomarkers are available. Here, we analyzed tumor samples from the METEOR trial to assess whether AXL expression predicts improved clinical outcomes with cabo relative to everolimus (evero, mTOR inhibitor) in patients (pts) with mccRCC. **Methods:** Double immunohistochemistry staining for AXL and CD45/CD163 (immune cell/ macrophage markers) was performed on 278 pretreatment tumor tissues from the METEOR trial (cabo=147; evero=131). Image analysis algorithms were used to assess the % of AXL+ tumor cells (TC), % of AXL+ immune cells (IC), and combined % of AXL+ TC and IC (TC/IC). Optimal cutoffs, based on the minimum p-value approach, were determined at the 17^{th}, 30^{th}, and 22^{nd} percentile for TC, IC, and TC/IC, respectively. The association with progression-free survival (PFS) was assessed using Cox regression adjusted for IMDC risk groups, the presence of bone metastases, and the number of previous VEGFR TKI treatments. The association with objective response rate (ORR) (cabo arm only due to low response rate in evero arm) was reported descriptively. **Results:** We observed a strong correlation between % AXL+ TC and % AXL+ IC (Spearman correlation coefficient 0.85; p-value <0.001). In the evero arm, high % AXL+ TC and high % AXL+ TC/IC were significantly associated with shorter PFS (median 1.9 vs. 4.1 months and 1.9 vs 4.2 months, respectively); a similar trend was observed for % AXL+ IC. In the cabo arm, % AXL+ TC, % AXL+ IC, and % AXL+ TC/IC were not associated with PFS or ORR (Table). The magnitude of increase in PFS for pts receiving cabo versus evero was larger in pts with high % AXL+ TC compared to pts with low % AXL+ TC (HR: 0.30 vs. 0.51, p-interaction=0.18) and in pts with high % AXL+ TC/IC compared to pts with low % AXL+ TC/IC (HR: 0.30 vs 0.53, p-interaction=0.12). **Conclusions:** Our finding that the improvement in outcome with cabo relative to evero is more evident in pts with high levels of AXL expression supports that the antitumor activity of cabo in mccRCC is mediated, in part, by AXL inhibition. Our work identifies AXL expression as a potential predictive biomarker for cabo-based therapies in mccRCC. Research Sponsor: NCI Dana Farber / Harvard Cancer Center Kidney Cancer SPORE; CDMRP Kidney Cancer Research Program; W81XWH2210523; Exelixis.

	Percent of AXL+ Cells (High vs Low)		
	Median PFS, month	HR PFS (95%CI)	ORR (%)
TC			
Cabozantinib	7.3 vs 7.2	1.26 (0.73, 2.15)	12% vs 15%
Everolimus	1.9 vs 4.1	2.15 (1.21, 3.82)	-
IC			
Cabozantinib	7.3 vs 7.3	0.93 (0.58, 1.50)	15% vs 14%
Everolimus	3.8 vs 4.0	1.42 (0.89, 2.27)	-
Combined TC/IC			
Cabozantinib	7.3 vs 7.3	1.14 (0.70, 1.87)	14% vs 14%
Everolimus	1.9 vs 4.2	1.99 (1.21, 3.27)	-

Anlotinib combined with sintilimab as first-line treatment in patients with advanced non-clear cell renal cell carcinoma (nccRR): Preliminary results from an exploratory prospective multicentre clinical study.

Pei Dong, Wensu Wei, Lijuan Jiang, Zhiling Zhang, Deling Wang, Yulu Peng, Tingxuan Huang, Xi Zhong, Shengjie Guo, Hui Han, Xiuyu Cai, Fangjian Zhou; Department of Urology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Urology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine, Guangzhou, China; Department of Medical Imaging, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of General Internal Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Non-clear cell renal cell carcinoma (nccRCC) accounts for approximately 25% of all kidney cancers, however, the effect of systemic chemotherapy is limited. We report the first results of a single-arm, phase 2 study (NCT05220267) evaluating the efficacy and safety of anlotinib (a multi-target tyrosine kinase inhibitor) combined with sintilimab (a monoclonal antibody against programmed cell death protein 1) as first-line treatment in patients with advanced nccRCC. **Methods:** Patients with histologically confirmed advanced nccRCC and measurable disease per RECIST v1.1 who had not previously received systemic therapy were received anlotinib (12 mg qd, d1-14, repeated every 21 days) plus sintilimab (200 mg IV Q3W) till disease progression or intolerant toxicity. The primary endpoint is progression-free survival (PFS); secondary endpoints include objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety. **Results:** From April 2022 to December 2023, 43 patients were enrolled with a median age of 43 years (range: 18-79), 10 (23.3%) had papillary histology, 10 (23.3%) had FH-RCC histology, 8 (18.6%) had TFE3-RCC histology and 15 (34.9%) were unclassified. Among these participants, 34 patients were evaluable. 62.8% were IMDC intermediate- or poor-risk, 74.4% had prior nephrectomy and 100% had synchronous metastatic disease. ORR and DCR were 52.9% (95%CI 0.35-0.70) and 94.1% (95%CI 0.80-0.99) , respectively.≥1 and <1 Combined Positive Score of PD-L1 expression were observed in 50.0% (17/34) and 32.4% (11/34) patients respectively, and the ORR was 52.9% (95%CI: 0.278-0.770) and 45.5% (95%CI: 0.167-0.766) in the two groups. The median time of the first response was 3.7 months (range, 3.3-9.5). As of January 7, 2024, median follow-up time was 8.5m (95%CI 4.8-12.3). The median PFS was 15.1m (95%CI 13.2-15.9). Treatment-related grade 3/4 adverse events were observed in 20.9% (9/43) of the patients, encompassed hyponatremia (3 patients, 7%), proteinuria (1 patients, 2%), anemia (1 patients, 2%), Hand-foot syndrome (4 patients, 9.1%). Neither unexpected safety signals nor treatment-related death occurred. **Conclusions:** Our results showed promising efficacy and acceptable toxicity of anlotinib plus sintilimab for patients with advanced nccRCC. Complete results are awaited in 2024 after follow-up completion of the entire cohort. Clinical trial information: NCT05220267. Research Sponsor: None.

4545 Poster Session

Biomarker analysis of zanzalintinib in clear cell renal cell carcinoma from STELLAR-001.

Sumanta Kumar Pal, Jacques Medioni, Guillermo de Velasco, Jaime R. Merchan, Tomáš Büchler, Andrea B Apolo, Yohann Loriot, Zhong Wang, Taylor Jew, Anthony Cao, Andrew Simmons, Robert J. Motzer; City of Hope Comprehensive Cancer Center, Duarte, CA; APHP Hôpital Européen Georges Pompidou and Université Paris Cité, Paris, France; Hospital Universitario 12 de Octubre, Madrid, Spain; University of Miami Miller School of Medicine, Miami, FL; Charles University and Thomayer University Hospital, Prague, Czech Republic; National Cancer Institute, Bethesda, MD; Institut de Cancérologie Gustave Roussy, Villejuif, France; Exelixis, Inc., Alameda, CA; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: Zanzalintinib (zanza) is a novel oral multi-targeted TKI that inhibits several receptors, including VEGFR, MET, and TAM kinases. In an expansion cohort of previously treated patients (pts) with clear cell renal cell carcinoma (ccRCC) from the phase 1b STELLAR-001 study (NCT03845166), single-agent zanza showed encouraging activity (ORR, 38%; disease control rate, 88%), with responses seen in VEGFR TKI–pretreated pts, and a manageable safety profile (Pal, IKCS NA 2023:Abs 1). Here, we investigate biomarkers associated with zanza from the STELLAR-001 ccRCC expansion cohort. **Methods:** Adult pts (N=32) with advanced ccRCC, ECOG ≤1, and 1–3 prior systemic anticancer therapies received zanza 100 mg once daily until unacceptable toxicity or no longer deriving clinical benefit. Circulating plasma biomarkers and immune cell populations in blood were assessed at baseline and on-study. IHC for AXL, c-Met, phosphorylated Met, and VEGFR2 was performed on archival tissue. Associations between response to zanza and biomarker levels (at baseline and treatment-related changes) were investigated by comparing zanza responders (CR/PR; n=10) and non-responders (SD/PD; n=19). The relation between baseline biomarker levels and prior exposure to VEGFR TKI was also evaluated. *P* values were determined using a Wilcoxon test ($P<0.05$ considered significant). **Results:** Zanza elicited significant changes in soluble biomarkers related to angiogenesis, tumor growth and metastasis, and immune modulation, including an increase in the circulating ligands VEGF ($P<0.001$) and GAS6 ($P<0.001$); decreases in ANG-1 ($P<0.001$) and ANG-2 ($P<0.001$), and the soluble angiogenic receptors, VEGFR2 ($P<0.001$) and TIE-2 ($P<0.001$). A decrease in levels of the chemokine, RANTES ($P<0.001$), and an increase in IFNγ ($P=0.039$) and the pro-apoptotic protein, granzyme B ($P<0.001$) were also observed. An analysis of immune cell subsets showed that zanza raised activated cytotoxic T cell numbers ($P=0.002$). Reductions in monocytes ($P=0.001$), along with immunosuppressive subsets (total MDSCs [$P=0.013$] and granulocytic MDSCs [$P=0.014$]) were also observed. Response to zanza was associated with lower baseline levels of plasma biomarkers including CRP ($P=0.025$) and HGF ($P=0.017$), but not with any tissue biomarkers or zanza-mediated changes in immune cells or plasma biomarkers tested. Lower baseline levels of VEGFR2 were observed in pts with prior VEGFR TKI exposure ($P=0.042$). **Conclusions:** Zanza in pts with advanced ccRCC leads to modulation of plasma biomarkers associated with angiogenesis and peripheral immune cell subsets consistent with its expected mechanism of action. The reduction in immunosuppressive immune cells and activation of effector immune cells by zanza support the rationale for combining zanza with immune checkpoint inhibitors. Given the small sample sizes, further investigation in larger studies is warranted. Clinical trial information: NCT03845166. Research Sponsor: Exelixis, Inc.

Molecular analysis of the HCRN GU16-260-Cohort A phase II study of first-line (1L) nivolumab (nivo) and salvage nivo + ipilimumab (ipi) in patients (pts) with advanced clear cell renal cell carcinoma (accRCC).

Jacob Peter Zaemes, Miya Hugaboom, Valisha Shah, Naomi B. Haas, David F. McDermott, Opeyemi Jegede, Mehmet Asim Bilen, Mark N. Stein, Jeffrey A. Sosman, Robert S. Alter, Elizabeth R. Plimack, Michael E. Hurwitz, Catherine J. Wu, David Johnson Einstein, Hans J. Hammers, Sabina Signoretti, Destiny West, Thomas Denize, Michael B. Atkins, David A. Braun; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Yale Cancer Center, Yale School of Medicine, New Haven, CT; University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Winship Cancer Institute of Emory University, Atlanta, GA; Columbia University Irving Medical Center, New York, NY; Northwestern University, Chicago, IL; Hackensack University Medical Center, Hackensack, NJ; Fox Chase Cancer Center, Philadelphia, PA; University of Texas Southwestern Harold C. Simmons Comprehensive Cancer Center, Dallas, TX; Brigham and Women's Hospital, Boston, MA; Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC

Background: Seven molecular subsets of ccRCC have been proposed: 1: Angiogenic/Stromal; 2: Angiogenic; 3: Complement/Ω-oxidation; 4: T-effector/Proliferative; 5: Proliferative; 6: Stromal/Proliferative; and 7: snoRNA (Motzer et al. Can Cell 2020). In an analysis of IMmotion 151, which compared 1L atezolizumab/bevacizumab to sunitinib, combination immune checkpoint blockade (ICB) and anti-VEGF therapy was associated with improved progression-free survival (PFS) and overall survival (OS) in clusters (CLs) 4 and 5, increased PFS in CL 7, and decreased OS in CL 2 (Motzer Can Cell 2020, Motzer JAMA Onc 2022). CL 4 was also associated with higher PFS and objective response rate (ORR) in >1L nivo compared to everolimus in an analysis of CheckMate-025 (Denize CCR 2022). To date, outcomes have not been compared among accRCC subtypes in pts who received 1L pure ICB. **Methods:** In HCRN GU16-260-Cohort A, pts with accRCC received 1L nivo monotherapy until progressive disease (PD), unacceptable toxicity, or completion of 96 weeks of therapy. Pre-treatment FFPE tumor samples were obtained. A machine learning model (random forest) was trained on annotated transcriptomic data from bulk RNA-seq and used to classify tumors that passed quality control into one of the 7 molecular subtypes. **Results:** 70 tumor samples contained adequate RNA quality and were classified as outlined in the table. IMDC rates and ORR (40%) for the RNAseq population closely matched those of the whole study (Atkins JCO 2022). No tumors were classified in CL 7 and only 3 in CL 5. Tumors in each IMDC group contained a mix of subtypes. The highest ORR occurred in CL 4 (6/10, 60.0%); CL 4 median PFS was 15.2 months and 1-year PFS was 60%. ORR was also high in CLs 1 and 3 at 52.4% and 40.0%, respectively and lowest in CL 2 (12.5%). PD as best response (5/10, 50.0%) and short PFS (5.1 months) were seen in CL 6. **Conclusions:** Consistent with prior analyses with combination ICB + anti-VEGF and >1L ICB, CL 4 was associated with robust 1L ICB monotherapy antitumor efficacy. Surprisingly, ORR was also high in CLs 1 and 3. In this small dataset, transcriptomic signatures enriched for but did not fully predict ORR. Future prospective trials are needed to identify more discriminative biomarkers of efficacy for pure ICB therapy. Research Sponsor: National Cancer Institute; U.S. Department of Defense; Dana-Farber/Harvard Cancer Center Kidney Cancer SPORE; Bristol Myers Squibb.

IMDC risk category and best ORR and PFS data by cluster.

CL	N	IMDC Fav (N,%) 21 Pts	IMDC Int (N,%) 44 Pts	IMDC Poor (N,%) 5 Pts	CR/PR (N,%) 28 Pts	SD (N,%) 21 Pts	PD (N,%) 21 Pts	Median PFS (Months)	1-Year PFS (%)
1	10	4 (19.0)	6 (13.6)	0 (0)	4 (40.0)	2 (20.0)	4 (40.0)	7.5	40.0
2	16	3 (14.3)	12 (27.3)	1 (20.0)	2 (12.5)	12 (75.0)	2 (12.5)	9.9	37.5
3	21	10 (47.6)	11 (25.0)	0 (0)	11 (52.4)	3 (14.3)	7 (33.3)	8.2	42.9
4	10	3 (14.3)	6 (13.6)	1 (20.0)	6 (60.0)	2 (20.0)	2 (20.0)	15.2	60.0
5	3	0 (0)	1 (2.3)	2 (40.0)	1 (33.3)	1 (33.3)	1 (33.3)	4.2	33.3
6	10	1 (4.8)	8 (18.2)	1 (20.0)	4 (40.0)	1 (10.0)	5 (50.0)	5.1	40.0

Association between circulating cytokines expression patterns and outcomes to immune-checkpoint (ICI)–based regimens in metastatic renal cell carcinoma (mRCC).

Laura Meili Linville, Ardit Feinaj, Kaizen Nathani, Nirmish Singla, Mark Yarchoan, Mark Christopher Markowski, Michael Anthony Carducci, Kabeer Munjal, Christopher Thoburn, Jennifer Gizzi, Chester Kao, Roy Elias, Yasser Ged; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: ICI combinations (combos) in the form of dual ICI or ICI plus tyrosine kinase inhibitors (TKI) combos currently represent the most effective therapies in mRCC patients (pts). However, there is an unmet need to discover biomarkers predictive of clinical benefit to ICI combos. Circulating cytokines are important regulators of the immune system and may contribute to cancer immunotherapy outcomes. In mRCC, prior studies showed that baseline cytokines expression may influences outcomes to ICI monotherapy, but this association is unknown in ICI combos. Herein, we examined the association between circulating cytokines and ICI combos in mRCC. **Methods:** We prospectively collected baseline blood samples from mRCC pts receiving ICI combos at our institution. Circulating cytokine profile was assessed using a 32-plex cytokine assay. Baseline demographic, clinical characteristics, and treatment outcomes were collected from electronic health record review. IMDC risk categories were determined at ICI combo initiation. Clinical benefit was defined as radiologic partial response, complete response, or stable disease $\geq$ 12 months. Median cytokine concentration was used to stratify cytokine expression levels (high vs. low). Univariate and multivariate logistic regression was used to evaluate cytokines expression with time to next treatment (TNT). **Results:** A total of 29 mRCC pts who received ICI combos were included. 76% were men with a median age of 66 years (IQR 37-80) and 69% had clear cell tumors. ICI combos included ICI+ICI in 15 pts (52%) and ICI+TKI in 14 pts (42%). Poor-risk according to IMDC classification was positively associated with IL-6 (p= 0.03) and IL-8 (p=0.01) baseline expression, while intermediate-risk was positively associated with IL-22 expression (p=0.028). 38% of pts had clinical benefit from ICI combos in our cohort. Clinical benefit was negatively associated with IL-8 (p=0.04), IL-10 (p=0.03) and VEGF-alpha (p=0.03) baseline expression. Pts with high IL-6, IL-8, IL-10, and VEGF-Alpha baseline expression had a median TNT of 5.09 vs. 17.32 months (p= 0.07), 5.32 vs. 17.32 months (p =0.09), 5.32 vs. 25.59 months (p=0.04), and 3.77 vs. not reached (NR) (p=0.00), respectively. Among pts with intermediate risk mRCC, those with high VEGF-alpha and IL-6 expression had a median TNT of 5.07 months vs. NR (p=0.00), and 5.32 vs.17.32 month (p=0.002) respectively. In multivariate COX regression analysis VEGF-alpha expression was found to be an independent risk factor for TNT (HR, 2.56, 95% CI, 1.27-5.18; P = 0.009). **Conclusions:** Baseline expressions of IL-6, IL-8, IL-10 VEGF-alpha, may represent an important prognostic biomarker that can further risk stratify intermediate risk mRCC and predict clinical outcomes to ICI combos. Analysis of the association between ICI combo outcomes and post-treatment cytokine profiles is in progress. Research Sponsor: None.

Association of baseline inflammatory biomarkers and clinical outcomes in patients with advanced renal cell carcinoma (aRCC) treated with immune checkpoint inhibitors (ICIs).

Ahmet Yildirim, Mengting Wei, Yuan Liu, Rohit Vivek Goswamy, Yujin Choi, Jacqueline T Brown, Bassel Nazha, Dylan J. Martini, Caitlin Hartman, Greta Russler McClintock, Tony Zhuang, Haydn Kissick, Wayne B. Harris, Bradley Curtis Carthon, Omer Kucuk, Viraj A. Master, Mehmet Asim Bilen; Winship Cancer Institute of Emory University, Atlanta, GA; Emory University, Atlanta, GA; Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA; Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; Department of Medicine, Massachusetts General Hospital, Boston, MA; Department of Medicine, Emory University School of Medicine, Atlanta, GA; Department of Urology, Emory University School of Medicine, Atlanta, GA

Background: Multiple inflammatory biomarkers such as modified Glasgow Prognostic Score (mGPS), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), and neutrophil to eosinophil ratio (NER) have been identified in RCC. We analyzed those biomarkers in patients with aRCC treated with ICIs to assess the association with treatment outcomes. **Methods:** A retrospective analysis was conducted on adult patients with aRCC treated with ICIs at Emory Winship Cancer Institute between 2018 and 2023. Clinical benefit (CB) is determined by stable disease, partial response, and complete response. mGPS (combining albumin and CRP), NLR, MLR, PLR, and NER data were collected from the baseline bloodwork. Multivariate and univariate analyses were conducted on PFS, OS, and CB. MVA was built by controlling the age, gender, race, BMI, smoking status, IMDC risk group, clear cell histology, prior treatment, liver metastases, ECOG performance score, and number of distant metastases, which were subject to backward elimination at the significant level of $p < 0.2$ **Results:** Our analysis included a total of 401 patients (118:283 F:M, median age: 66). On univariate analysis, high mGPS, NLR, MLR, PLR, and NER were related to inferior CB; hazard ratios (HR) (95% CI, p value) were 3.03 (1.35-6.77, p=0.005), 1.86 (1.14-3.03, p=0.013), 1.83 (1.10-3.02, p=0.019), 2.37 (1.52-3.71, p <.001), 1.93 (1.22-3.05, p=0.005) respectively. On multivariate analysis, NLR, PLR, NER had statistically significant correlation with CB, HR (95% CI) were 1.75 (1.01-3.04, p=0.047), 2.21 (1.33-3.66, p=0.002), 2.07 (1.24-3.47, p=0.006). **Conclusions:** The results demonstrated that high systemic inflammatory biomarkers may be related to worse clinical outcomes with ICI treatment. Prospective studies are needed for further validation. Research Sponsor: None.

		UVA OS		UVA PFS		MVA OS		MVA PFS	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
	0 n:96	0.29 (0.19-0.45)		0.42 (0.28-0.62)		0.37 (0.20-0.67)		0.43 (0.29-0.65)	
mGPS	1 n:85	0.72 (0.48-1.08)	**<.001**	0.67 (0.45-0.98)	**<.001**	0.97 (0.58-1.63)	**<.001***	0.66 (0.44-0.98)	**<.001**
	2 n:43	-		-		-		-	
NLR[a]	≥5.103	0.55 (0.42-0.73)	**<.001**	0.64 (0.50-0.82)	**<.001**	0.72 (0.51-1.01)	0.056	0.71 (0.53-0.95)	**0.021**
MLR[b]	≥0.630	0.45 (0.34-0.60)	**<.001**	0.56 (0.44-0.72)	**<.001**	0.60 (0.44-0.83)	**0.002**	0.69 (0.53-0.90)	**0.007**
PLR[c]	≥202.381	0.62 (0.48-0.81)	**<.001**	0.64 (0.51-0.80)	**<.001**	1.01 (0.74-1.39)	0.938	0.81 (0.62-1.06)	0.125
NER[d]	≥43.083	0.60 (0.45-0.78)	**<.001**	0.63 (0.50-0.80)	**<.001**	0.63 (0.46-0.87)	**0.004**	0.65 (0.50-0.85)	**0.001**

[a]:High NLR ≥5.103 (n:106, 26.6%), Low NLR <5.103 (n:293, 73.4%).
[b]:High MLR ≥0.630 (n:103 25.8%), Low MLR <0.630 (n:296 74.2%).
[c]:High PLR ≥202.381 (n:180 45.1%), Low PLR <202.381 (n:219 54.9%).
[d]: High NER ≥43.083 (n:135 33.9%), Low NER <43.083 (n:264 66.1%).

Examination of irAE and treatment discontinuation irAE in patients with RCC with T effector phenotype.

Catherine Fahey, Anupama Reddy, Kristin Kathleen Ancell, Kerry Roe Schaffer, Brian I. Rini, Katy Beckermann; Vanderbilt University Medical Center, Nashville, TN; Vindhya Data Science, Durham, NC

Background: The standard of care for renal cell carcinoma (RCC) is physician-choice of dual immunotherapy with ipilimumab/nivolumab (IO/IO) or a combination a VEGF inhibitor with immunotherapy (VEGF/IO). The IMmotion 151 trial identified gene expression signatures that differentiate likelihood of response to IO/IO (cluster 4 and 5 – T effector) versus VEGF/IO (cluster 1 and 2 - Angiogenic). Given that the T effector RNA-seq signature consists of higher expression of genes associated with inflammation, we hypothesized that patients with the T effector phenotype would have higher rates of immune-related adverse events (irAE) on IO-based therapy. **Methods:** Patients with metastatic RCC treated with systemic IO-based therapy had RNA sequencing completed on the primary tumor or metastatic site. Charts of patients who had a T effector RNA-seq signature were manually curated to identify development of irAE by reading the most recent clinic note and searching ‘steroids’, ‘irAE’, ‘rash’, ‘thyroid’. Hits from searches were investigated by manual chart review. **Results:** 118 patients underwent RNA sequencing and 105 passed quality control. Nineteen patients (18%) were assigned the T effector phenotype. Of the 17 metastatic patients, twelve of these patients received at least one dose of IO/IO in the first or second line of therapy, five were treated with VEGF/IO Among patients treated with IO/IO, 8 developed any grade irAE (66%; 41% grade 3+), 5 (41%) required steroid treatment, 5 (41%) required hospitalization, and 4 (33%) discontinued treatment due to irAE. Grade 3 toxicities in this group included colitis, adrenal insufficiency, and hypophysitis. Of the 5 patients treated with VEGF/IO, 3 developed any grade irAE (60%; 20% grade 3+), none were treated with steroids, and none were hospitalized. The grade 3 toxicity in this group was adrenal insufficiency. **Conclusions:** Patients with a T effector RNA-seq signature had higher rates ofirAE than historic controls when treated with IO/IO leading to high rates of steroid use and treatment discontinuation. VEGF/IO-treated patients with the T effector RNA-seq signature had similar rates of irAE to historic controls. The ongoing OPTIC clinical will expand on these results by studying treatment assignment in a prospective manner. Research Sponsor: National Cancer Institute; T32CA217834.

Impact of CBM588 on gut microbiome composition and dysbiosis in patients receiving frontline immune checkpoint inhibitor (ICI) combinations for metastatic renal cell carcinoma (mRCC).

Nazli Dizman, Hedyeh Ebrahimi, Regina Barragán Carrillo, Luis A Meza, Paulo Gustavo Bergerot, Tanya B. Dorff, Joann Hsu, Zeynep Busra Zengin, Daniela V. Castro, Alex Chehrazi-Raffle, Abhishek Tripathi, Jeffrey M. Trent, Motomichi Takahashi, Kentaro Oka, Seiya Higashi, Gregory Caporaso, Keehoon Lee, Sumanta Kumar Pal; The University of Texas MD Anderson Cancer Center, Houston, TX; City of Hope Comprehensive Cancer Center, Duarte, CA; Oncoclinicas & Co - Medica Scientia Innovation Research (MEDSIR), São Paulo, Brazil; Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; TGen, Phoenix, AZ; Miyarisan Pharmaceutical Co., Ltd., Saitama, Japan; Translational Genomics Institute, Phoenix, AZ; Translational Genomics Research Institute (TGen North), Flagstaff, AZ

Background: Two recent randomized phase I clinical trials have provided compelling evidence that CBM588, a *Clostridium butyricum*-based live biotherapeutic, holds potential to enhance clinical outcomes in patients with mRCC receiving frontline ICI combinations (Dizman *et al*Nature Medicine 2022; Ebrahimi *et al*ASCO 2023). We examined the impact of CBM588 on gut microbiome composition in a combined cohort of these two studies to further investigate its impact on gut microbiome. **Methods:** We analyzed stool samples from two phase I randomized clinical trials that enrolled patients with mRCC treated with (1) nivolumab/ipilimumab (nivo/ipi) +/- CBM588 and (2) cabozantinib/nivolumab (cabo/nivo) +/- CBM588. We compared gut microbiome diversity and composition at baseline and week 12 between patients in the standard of care (SOC) arms (nivo/ipi or cabo/nivo) and those who received CBM588 in combination with a SOC regimen (SOC/CBM). Taxonomic profiling was performed using MetaPhlan v4, and changes in the abundances of clinically relevant microbial species from baseline to week 12 were assessed using the Wilcoxon matched pairs test. The ratio of Firmicutes/Bacteroidetes, a measure of gut dysbiosis, was computed across time points in the two cohorts. **Results:** Among 58 patients included in the analysis, 38 received SOC/CBM588 as first-line treatment. The median age of the overall cohort was 60 years (range: 36-90). The majority were male (71%), had clear cell mRCC (88%), and intermediate/poor risk disease (79%). In both the SOC and SOC/CBM cohorts, there were no statistically significant differences in alpha and beta diversity between baseline and week 12. Among clinically relevant species compared between baseline and week 12, *Alistipes senegalensis* decreased in both the SOC and SOC/CBM cohorts (log fold change [LFC] -0.82 [P=0.004] and LFC -0.36 [P=0.007], respectively), while *Eubacterium siraeum* decreased only in the SOC cohort (LFC -1.75 [P=0.005]). The Firmicutes/Bacteroidetes ratio increased from 89.0% to 96.4% in the SOC cohort, whereas a notable decrease was observed in this ratio from 100.0% to 75.7%. in the SOC/CBM cohort. **Conclusions:** Supplementation with CBM588 leads to a marked correction of gut dysbiosis and prevents the depletion of species previously associated with ICI response (i.e., *Eubacterium siraeum*). These findings provide a plausible mechanism for the enhanced clinical outcome with CBM588 now seen across two small, randomized trials. A phase III study is planned within the cooperative groups to evaluate the clinical activity and gut microbiome modulation capacity of CBM588 in combination with ICIs in mRCC. Research Sponsor: None.

Applying genomic analysis to refine unclassified renal cell carcinoma.

Emre Yekeduz, David A. Braun, Razane El Hajj Chehade, Marc Eid, Chris Labaki, Marc Machaalani, Amin Nassar, Rashad Nawfal, Eddy Saad, Renee Maria Saliby, Karl Semaan, Maxine Sun, Michelle S. Hirsch, Yüksel Ürün, Talal El Zarif, Toni K. CHOUEIRI; Dana-Farber Cancer Institute, Boston, MA; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Department Medicine, Beth Israel Deaconess Medical Center, Boston, MA; Yale Cancer Center, New Haven, CT; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Department of Medical Oncology, Ankara University School of Medicine, Ankara, Turkey; Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

Background: Despite the improvements in genomic and pathological techniques to identify renal cell carcinoma (RCC), 2-6% of all patients with RCC cannot be classified into a particular subgroup, thus called "unclassified" RCC (uRCC). Ascertaining the genomic profile of those patients may help select proper treatment and find novel targets. **Methods:** The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database v15.0 was used to select patients with RCC by using the OncoTree codes. All included patients were divided into four groups based on the most frequent subtypes of RCC: clear cell RCC (ccRCC), papillary RCC (pRCC), chromophobe RCC (chRCC), and uRCC. The Cancer Genome Atlas (TCGA) was additionally used to assess corresponding oncogenic signaling pathways. We employed the chi-squared test to compare categorical variables and applied the Benjamini-Hochberg correction to calculate Q-values, thereby controlling the false discovery rate. **Results:** Overall, 1,990 tumor samples from 1,888 patients were evaluated. uRCC was observed in 184 patients (9.7%), whereas most had ccRCC (n=1339, 70.9%), followed by pRCC (n=224, 11.9%) and chRCC (n=141, 7.5%). Age distribution at sample sequencing was comparable between uRCC and other RCC subtypes ($P>0.05$). The proportion of female patients with uRCC was higher at 38.4%, compared to 26.5% in ccRCC (Q=0.002) and 16.3% in pRCC ($Q<0.001$), yet was comparable to chRCC at 48.6% (Q=0.210). The prevalence of uRCC was also greater among black patients, accounting for 8.6% vs. 2.1% in ccRCC (Q=0.001). Among patients with uRCC (n=224), the most common genomic alterations (GAs) were detected in *NF2* (15.8%), *SETD2*(15.8%), *TP53 (13.9%)*, *TERT*(13.4%), and *VHL*(11.8%). *NF2* alterations were also more prevalent in patients with uRCC than in patients with ccRCC (1.8%, $Q<0.001$), chRCC (0.7%, $Q<0.001$), and pRCC (5.8%, Q=0.058). Notably, median overall survival (OS) was poorer in uRCC patients with altered *NF2*(n=29)than in those with unaltered *NF2*(n=155, 30.7 vs. 87.1 months, p=0.058). Of patients with uRCC, 135 (72.5%) samples were from primary tumors and 39 (20.9%) from metastatic sites, with no difference in GA frequencies between the two. *CDKN2A* and *CDKN2B* were the most frequent co-mutated genes in uRCC ($Q<0.001$), followed by *VHL* and *BAP1* ($Q<0.001$), and *SETD2* and *PBRM1* (Q=0.023). GAs in uRCC were primarily observed in pathways related to TP53 (42.8%), cell cycle (33.3%), PI3K (23.5%), and HIPPO (7.7%). **Conclusions:** uRCC exhibited a unique genomic profile distinct from other common RCC subtypes.Notably, *NF2*alterations were frequent and correlated with a poorer prognosis. Research Sponsor: None.

Frequent Genomic Alterations in uRCC (n=184,%)	
NF2	29 (15.85%)
SETD2	29 (15.85%)
TP53	26 (13.98%)
TERT	24 (13.48%)
VHL	22 (11.89%)
BAP1	21 (11.48%)
PBRM1	14 (7.82%)
MTOR	13 (7.10%)
FAT1	12 (6.90%)

Genomic landscape of metastatic clear cell renal cell carcinoma (mccRCC): A retrospective real-world analysis from Flatiron Health (FH)-Foundation Medicine, Inc. (FMI) clinico-genomic database (CGDB).

Mimma Rizzo, Gaetano Pezzicoli, Camilla Porta, Massimiliano Povero, Lorenzo Pradelli, Emilia Sicari, Valentina Sara Barbiero, Camillo Porta; Division of Medical Oncology, AOU Consorziale Policlinico di Bari, Bari, Italy; Interdisciplinary Department of Medicine, University of Bari 'Aldo Moro', Bari, Italy; AdRes Health Economics and Outcome Research, Turin, Italy; Roche SpA, Monza, Italy; University of Bari 'Aldo Moro' and AOU Policlinico di Bari, Bari, Italy

Background: Although the genomic landscape of mccRCC has been already documented in the literature, previous clinico-genomic studies have been constrained by small sample sizes, or a narrow focus on specific genes. In this large-scale study, we aimed at investigating the real-world frequency and co-occurrence of genomic alterations (GAs) detected in mccRCC samples. **Methods:** This study used the nationwide (US-based) de-identified FH-FMI CGDB. The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). Eligible patients (pts) were adults diagnosed with mccRCC, with FH-EHR records between January 1, 2011 and December 31, 2022. GAs were identified in the same time span via comprehensive genomic profiling using FMI tests on tumor tissue and blood samples. Co-occurrence and mutual exclusivity were assessed using Fisher's exact test, with multiple testing correction. Clustering analysis was performed on the gene network graph derived from significant interactions. **Results:** Out of 1,409 pts with renal cell carcinoma, 923 (65.5%) mccRCC were considered, with a median age at the diagnosis of metastatic disease of 61 years (IQR: 54-69). The majority were male (70.3%) and white (71.1%). Nearly 89% (822) received systemic therapy, with a median number of 2 treatment lines (IQR: 1-4). A total of 958 samples were sequenced, of which 92.2% were performed on tissue, and 7.8% on blood. GAs (81.1% short variant, 17.1% copy number variant, and 1.8% rearrangement) were found in 246 different genes, with a median number of mutated genes per pts of 3 (IQR: 2-5), while in 22 (2.4%) pts, no GAs were detected. *VHL* (69.7%), *PBRM1* (39.9%), *SETD2* (24.2%), *CDKN2A* (19.0%), *BAP1* (15.6%), *CDKN2B*(14.8%), *TP53* (14.1%), *KDM5C* (13.5%), *PTEN* (11.2%), and *TERT* (8.7%) were the top-10 mutated genes. Tumor Mutational Burden (TMB) was evaluated in 639 tissue samples, with a median value of 2.6 mut/Mb; 1.6% only of the tumors studied had high TMB. Out of the 796 samples examined for microsatellite instability (MSI), only 0.6% harbored MSI-intermediate, and none showed MSI-high. Co-occurrence analysis revealed 32 significant gene interactions. *CDKN2A/B* were significantly associated with *MTAP*, *BAP1*, and *NF2*, while *PBRM1* was enriched with *VHL*, *SETD2*, *KDM5C*, and *MTOR. TSC1*co-occurred with *TERT*, *TP53*, and *VHL.*Three clusters of co-occurring genes were identified: (1) *VHL*, *SETD2*, *PBRM1*, *KDM5C*, *MTOR*, and *NFE2L2*; (2) *TP53*, *TSC1*, and *TERT*; (3) *CDKN2A*, *CDKN2B*, *BAP1*, *NF2*, *MTAP*, and *ARID1A*. Mutually exclusive patterns were observed between cluster 1 and cluster 3 genes. Notably, *BAP1* was mutually exclusive with *PBRM1*. **Conclusions:** This is the largest analysis of the genomic landscape of mccRCC. We identified 3 clusters of co-occurring genes, whose prognostic/predictive value will be object of future research. Research Sponsor: Roche SpA.

Identification of prognostic genomic biomarkers in metastatic clear cell renal cell carcinoma (mccRCC): An analysis of the large retrospective real world clinico-genomic data from Flatiron Health (FH)-Foundation Medicine, Inc. (FMI) clinico-genomic database (CGDB).

Mimma Rizzo, Gaetano Pezzicoli, Camilla Porta, Massimiliano Povero, Lorenzo Pradelli, Emilia Sicari, Valentina Sara Barbiero, Camillo Porta; Division of Medical Oncology, AOU Consorziale Policlinico di Bari, Bari, Italy; Interdisciplinary Department of Medicine, University of Bari 'Aldo Moro', Bari, Italy; AdRes Health Economics and Outcome Research, Turin, Italy; Roche SpA, Monza, Italy; University of Bari 'Aldo Moro' and AOU Policlinico di Bari, Bari, Italy

Background: Despite a number of therapeutic improvements, mccRCC still has a poor prognosis, with limited prognostic predictors for clinical practice. The aim of this study was to evaluate the prognostic value of three clusters of co-occurring genes in mccRCC. **Methods:** We conducted a retrospective analysis of adult patients with mccRCC who were profiled by performing FMI genomic tests using tissue biopsies or blood samples. Data were from the nationwide (US-based) de-identified FH-FMI CGDB, originating from approximately 280 US cancer clinics (~800 sites of care). Patients diagnosed from January 01, 2011 to June 30, 2022 were followed until death or the last available observation (within December 31, 2022). Overall Survival (OS) was estimated using the Kaplan-Meier methods, while Cox proportional hazard model with risk set adjustment was used to assess the prognostic role of three pre-specified clusters of co-occurring genes; cluster 1 (C1) included *VHL*, *SETD2*, *PBRM1*, *KDM5C*, *MTOR*, and *NFE2L2*, cluster 2 (C2) included *TP53*, *TSC1*, and *TERT*, while cluster 3 (C3) included *CDKN2A*, *CDKN2B*, *BAP1*, *NF2*, *MTAP*, and *ARID1A*. Patients were considered cluster-positive (+) if they exhibited mutations in at least one gene within the cluster, and none in the other clusters. **Results:** 789 mccRCC patients were included [median age: 61 years, male: 71.1%, white race: 71.2%]. Among the 720 (91.3%) treated patients, 516 (71.7%) and 59 (8.2%) were classified per IMDC score as poor/intermediate and favorable risk, respectively (145 missing). Overall, almost half (45.5%; 359) were profiled after the diagnosis of metastasis (median gap time of 7.9 months) and 29 (3.7%) underwent multiple profile assessments, resulting in a total of 818 specimens analyzed. 332 (42.1%), 27 (3.4%), and 32 (4.1%) patients were C1+, C2+, and C3+, respectively. Median OS was 37 months (95% CI: 34-42). C1+ patients had higher OS compared to C1- (median OS: 50 vs. 30 months; HR: 0.57, $p<0.001$), while C3+ was associated with worse OS (median OS: 38 vs. 20 months; HR: 1.94, p=0.004). No association was found between C2 and OS (HR: 1.27; p=0.4). C1+ patients were more frequently classified as favorable risk compared to C1- (10.2% C1+ vs. 6.8% C1-, p=0.046) and they had longer duration of first-line (L1) treatment (median DoT: 9 vs. 7 months, p = 0.02). No significant differences between C2+ and C2-, C3+ and C3- patients were observed in L1 duration and IMDC distribution. **Conclusions:** This large-scale study identified two independent prognostic gene clusters in mccRCC. Further analyses will focus on the validation of the predictive role of these biomarkers with the ultimate aim of helping us develop tailored treatment strategies. Research Sponsor: Roceh SpA.

Disparate outcomes among Latino and non-Hispanic White (NHW) patients with metastatic clear cell renal cell carcinoma (mccRCC).

Sharon Choi, John Bliamptis, Justine Panian, Regina Barragán Carrillo, Skylar Reid, Thomas O'Keefe, Kripa Guram, Suzanna Lee, Sumanta Kumar Pal, Brent Shane Rose, Aditya Bagrodia, Ithaar Derweesh, Rana R. McKay; University of California, San Diego, San Diego, CA; University of California, San Diego, Moores Cancer Center, La Jolla, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; University of California, San Diego, La Jolla, CA; Univeristy of California San Diego, Department of Urology, La Jolla, CA; University of California, San Diego Health, La Jolla, CA; Moores Cancer Center at UC San Diego Health, La Jolla, CA

Background: Some studies have demonstrated that Latino patients (pts) with mccRCC have worse clinical outcomes than NHW pts. It is unclear if this disparity is related to biological differences and/or social determinants of health (SDOH). Herein, we investigate clinical-genomic features and outcomes among Latinos and NHW pts with ccRCC. **Methods:** Pts with mccRCC treated at UCSD were retrospectively identified from an institutional database. Pts with genomic sequencing on tumor tissue samples were included. Pts were categorized as Latino or NHW based on self-identification. Logistic regression was applied for the presence of divergent frequencies of somatic mutations. Cox regression models evaluated the effect of additional factors, including tumor genomic alterations and clinical features, on overall survival (OS). **Results:** The analysis included 135 pts with mccRCC, of whom 62 were Latinos. There were no significant differences in age at diagnosis (61 vs 62 years), BMI (28 in both), sex (76% vs 71% males), presence of sarcomatoid/rhabdoid features (38% vs 30%), and number of metastatic sites (71% vs 68% with >1 site). Compared to NHW, Latino pts had higher rates of IMDC intermediate/poor risk disease (85% vs 59%, $p<0.01$) and synchronous metastatic disease (60% vs 41%, p=0.04). Latino pts were also more likely to have public health insurance (42% vs 8%, $p<0.01$), and reside in areas with higher deprivation indexes (43% vs 20%, $p<0.01$). *BAP1* (26% vs 10%, p=0.02) and *ATM*mutations (10% vs 0%, $p<0.01$) were more common in Latino pts, whereas *SETD2* (32% vs 8%, $p<0.01$) and *TERT* alterations (19% vs 6%, p=0.04) were more prevalent among NHWs. *VHL*(84% vs 78%), *PBRM1* (27% vs 36%) and *TP53* (10% vs 14%) mutation rates were comparable between Latino and NHW pts. The use of first-line immune checkpoint inhibitor (ICI) based combination therapy was similar between groups (47% in both). In those receiving first-line ICI-based therapy, 2-year OS was shorter among Latino pts compared to NHW pts (HR 4.05, p=0.04). Similarly, Latino pts had a significantly reduced 2-year OS when treated with first-line tyrosine kinase inhibitor (TKI) monotherapy compared to NHW pts (HR 9.25, p=0.03). On multivariable analysis, there was a significant difference in OS between Latino and NHWs (HR 2.7, 95%CI 1.18-6.36, p=0.02) after adjusting for age, nephrectomy status, IMDC risk group, sarcomatoid features, synchronous disease, sites of metastasis, and *BAP1*, *PBRM1*, *SETD2*, *TP53*, *TERT,* and *KDM5C* mutations. **Conclusions:** Our study demonstrates that, within our local healthcare system, Latino pts with mccRCC present with different clinical-genomic features and worse survival outcomes. These findings underscore the complex interplay between tumor biology and SDOH. Our study emphasizes the unmet need to promote diversity in future research as well as understand and bridge disparities gaps across varied ethnicities with RCC. Research Sponsor: None.

Association of immune-related adverse events, inflammatory biomarkers, and clinical outcomes in patients treated with ICIs for advanced renal cell carcinoma.

Ahmet Yildirim, Mengting Wei, Yuan Liu, Rohit Vivek Goswamy, Yujin Choi, Jacqueline T Brown, Bassel Nazha, Dylan J. Martini, Caitlin Hartman, Greta Russler McClintock, Tony Zhuang, Haydn Kissick, Wayne B. Harris, Bradley Curtis Carthon, Omer Kucuk, Viraj A. Master, Mehmet Asim Bilen; Winship Cancer Institute of Emory University, Atlanta, GA; Emory University, Atlanta, GA; Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA; Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; Department of Medicine, Massachusetts General Hospital, Boston, MA; Department of Urology, Emory University School of Medicine, Atlanta, GA

Background: Immune Checkpoint Inhibitors (ICIs) have been the mainstay treatment for advanced renal cell carcinoma (aRCC). However, irAEs are still a challenge in clinical practice. We tested irAEs with inflammatory biomarkers and their association with clinical outcomes. **Methods:** A retrospective analysis was conducted on adult patients with aRCC treated with ICIs at Emory Winship Cancer Institute between 2018 and 2023. irAEs determined by the primary oncologist and reported by CTCAE v5.0. Univariate and multivariate analyses were conducted to determine the association between race, gender, OS, PFS, clinical benefit (CB, stable disease, partial response, complete response), modified Glasgow Prognostic Score (mGPS), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), neutrophil to eosinophil ratio (NER), and any grade irAE. MVA was built by controlling gender, race, smoking status, and prior treatment. **Results:** We analyzed 401 patients; 191 (47.6%) patients experienced any grade irAEs, with 41 (21.5%) of those classified as grade 3 or higher. Of 401 patients, 139 (34.6%) were treated with PD-1 inhibitor (PD-1i) monotherapy, 131 (32.6%) with PD-1i and CTLA-4 inhibitor combination, 108 (26.9%) with PD-1i and tyrosine kinase inhibitor combination. The median follow-up time was 43.0 months (36.5-51.3). On univariate analysis, the incidence of irAEs was higher in females than males (Odds ratio (OR),1.66 (1.08-2.57), p=0.021), White patients had a higher incidence of irAEs compared to African American patients (OR 2.20 (1.32-3.66), p=0.009). On multivariate analysis, low mGPS was correlated with a higher risk of irAEs (OR for mGPS of 0-1-2 was 6.03 (2.07-17.62), 3.75 (1.31-10.70), and reference respectively; p=0.004). irAEs were correlated with greater CB (OR 2.56 (1.53-4.29); p <.001), longer OS (HR 0.55 (0.37-0.82); p=0.003), and longer PFS (HR 0.51 (0.37-0.71); p <.001). **Conclusions:** Female patients, White patients, and patients with low inflammatory biomarkers may have a higher likelihood of experiencing irAEs. Patients who experienced irAEs may have better outcomes. Future prospective trials are needed for further evidence. Research Sponsor: None.

	mGPS			NLR		MLR		PLR		NER	
	0	**1**	**2**	**<5.103**	**≥5.103**	**<0.630**	**≥0.630**	**<202.38**	**≥202.38**	**<43.083**	**≥43.083**
irAE N	38 (40%)	45 (53.6%)	37 (86%)	141 (48.3%)	67 (63.8%)	145 (49.2%)	63 (61.8%)	108 (48.6%)	102 (57%)	127 (48.3%)	81 (60.5%)
irAE Y	57 (60%)	39 (46.4%)	6 (14%)	151 (51.7%)	38 (36.2%)	150 (50.8%)	39 (38.2%)	112 (51.4%)	77 (43%)	136 (51.7%)	53 (39.5%)
Odds Ratio (95% CI)	9.25 (3.56-24.04)	5.34 (2.04-14.00)	-	1.89 (1.19-2.99)	-	1.67 (1.05-2.65)	-	1.40 (0.94-2.08)	-	1.64 (1.07-2.50)	-
p value*		**<.001**		**0.007**		**0.029**		0.097		**0.022**	

Univariate analysis, *Type 3 p-value. The parametric p-value is calculated by ANOVA for numerical covariates and chi-square test for categorical covariates.

Comparative effectiveness of first-line (1L) ipilimumab plus nivolumab (Ipi + Nivo) versus immune checkpoint inhibitors + tyrosine kinase inhibitors (ICI + TKI) in patients (pts) with intermediate or poor (I/P) risk metastatic clear cell renal cell carcinoma (mccRCC).

Micah Ostrowski, Yeonjung Jo, Georges Gebrael, Chadi Hage Chehade, Arshit Narang, Gliceida Galarza Fortuna, Vinay Mathew Thomas, Beverly Chigarira, Ethan Anderson, Archisman Mazumder, Zeynep Irem Ozay, Neeraj Agarwal, Benjamin L. Maughan, Umang Swami; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Huntsman cancer insititute, University of Utah, Salt Lake City, UT; University of Utah/Huntsman Cancer Institute, Salt Lake City, UT; Gazi University Faculty of Medicine, Ankara, Turkey; Huntsman Cancer Institute, Salt Lake City, UT

Background: Ipi + Nivo or ICI + TKI are the 1L approved treatments for I/P risk mccRCC. In their respective registration trials, they were all compared to single-agent TKI. The comparative effectiveness of Ipi + Nivo vs. ICI + TKI has not been reported. Herein, we use a large real-world database to compare survival outcomes of pts receiving 1L Ipi + Nivo vs. ICI + TKI. **Methods:** This IRB approved retrospective study used the nationwide Flatiron Health electronic health record database. The de-identified data originated from approximately 280 cancer clinics (~800 sites of care). Inclusion: (1) pts with metastatic RCC with clear cell histology (2) I/P risk disease per IMDC criteria (3) Receipt of 1L treatment (Rx) with Ipi + Nivo or ICI + TKI (i.e. axitinib + pembrolizumab, cabozantinib + nivolumab, lenvatinib + pembrolizumab or axitinib + avelumab) between 11-08-2016 to 1-27-2023. Pts were classified into two groups based on Rx with Ipi + Nivo or ICI + TKI. Endpoints: Real-world overall survival (rwOS) and real-world time to next therapy (rwTTNT), summarized via Kaplan-Meier survival estimates with 95% confidence interval (CI) and compared in the context of propensity score (PS) matching weighted analysis and Cox proportional hazard model (PSM- CoxHzM). PS model included baseline covariates: age, race, smoking status, practice type, insurance, year of 1L, IMDC risk factors (all six), and missingness of covariates. All analysis done using R version 4.2.3. **Results:** Of 12,285 pts with mRCC in the dataset, 1033 met eligibility and were included (564 pts: Ipi + Nivo and 469 pts: ICI + TKI). The median rwOS for Ipi + Nivo was 30 months (mo) [95% CI 26 – 35] vs. 34 mo [95% CI 28 – 41] for ICI + TKI (HR 1.02, 95% CI 0.84 – 1.24, p = 0.81). The median rwTTNT was 9.1 mo [95% CI 8 – 11] for Ipi + Nivo vs. 15 mo [95% CI 14 – 18] for ICI + TKI (HR 1.29, 95% CI 1.09 – 1.51, p = 0.002). After PS matching, no significant difference in rwOS was noted between both groups (HR 1.01, 95% CI 0.83 – 1.24, p = 0.89). However, rwTTNT was significantly shorter with Ipi + Nivo compared to the ICI + TKI (HR 1.24, 95% CI 1.05 – 1.47, p = 0.011). **Conclusions:** In this study rwOS was comparable between pts receiving Ipi + Nivo vs. ICI + TKI Rx while rwTTNT was better with ICI + TKI. These data can help clinicians in pts counseling, and treatment selection. In the absence of validated biomarkers, the choice of 1L Rx for pts mccRCC should primarily depend on clinical factors (performance status, comorbidities, pt compliance and preference), Rx characteristics (toxicity profile) and disease status (urgency of response). Research Sponsor: None.

Unraveling the gene expression signatures with associated clinical outcomes in papillary renal cell carcinoma.

Juan Antonio Raygoza Garay, Samragnyi Madala, Matthew Robert Kroll, George Daniel Grass, Sumati Gupta, Laura Graham, Eric Kauffman, Jennifer King, Zin Myint, Paul Vincent Viscuse, Saum Ghodoussipour, Sean Kern, Adanma Ayanambakkam, Bodour Salhia, Michelle Churchman, Eric A. Singer, Yousef Zakharia; Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; Division of Hematology and Oncology, University of Iowa Hospitals and Clinics, Iowa City, IA; Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; University of Colorado Cancer Center Anschutz Medical Campus, Aurora, CO; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; University of Kentucky, Lexington, KY; Emily Couric Clinical Cancer Center, University of Virginia Health, Charlottesville, VA; Section of Urologic Oncology, Rutgers Cancer Institute of New Jersey and Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; Center for Prostate Disease Research (CPDR), Uniformed Services University, Bethesda, MD; Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Translational Genomics, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Aster Insights, Tampa, FL; The Ohio State University Comprehensive Cancer Center, Columbus, OH; University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA

Background: Papillary renal cell carcinoma (pRCC) is the second most common subtype of renal cancer. It is further subdivided into type I and type II, with type II being more aggressive. Previous analysis by the Cancer Genome Atlas (TCGA) Research Network suggested the clustering of pRCC tumors with *MET* alterations, *CDKN2A* silencing, *SETD2* mutations, *TFE3* fusions, and increased expression of the NRF2-antioxidant response element pathways. Nevertheless, there exists a gap in understanding the impact of altered molecular pathways or gene characteristics on the clinical outcomes of pRCC patients. Our study aims to explore gene expression signatures utilizing the Oncology Research Information Exchange Network (ORIEN) database and their associations with overall survival (OS) patterns in individuals diagnosed with pRCCs. **Methods:** Through whole RNA sequencing of kidney tumor tissue we examined the genes whose expression was associated with OS. Gene expression data were quantified using salmon and summarized at the gene level. Gene Expression batch correction was performed to remove technical sources of variation, and the vst normalized expression values were used in subsequent analyses. Time to event was defined as the time of the last contact – the time of tissue collection for sequencing. Univariate survival analysis was performed using the Cox-proportional hazards model (R survival package), correcting for Age, Sex, and Race. **Results:** The cohort consisted of 107 individuals with RNASeq and time-to-event data. 79% of individuals were male. The individuals had a median age of 69 years (IQR 61-72). After p-value adjustment (False Discovery Rate), two genes were significantly associated with OS (fdr$\leq$ 0.05). The first gene was *YTHDF2*, inversely associated with survival, having a hazard ratio of 0.002 95% CI [0.0289 - 0.0002], p-value= 0.025. Previous studies suggested this gene overexpressed in several cancers relative to adjacent normal tissue, whereas its expression was reduced in pRCC in the TCGA dataset. The second gene, *SEC31A*, is also negatively associated with OS, with a hazard ratio of 0.02 95% CI [0.0289 - 0.0002], p-value= 0.0001. SEC31A is an outer coat protein complex II (COPII) component associated with pRCC and other papillary-type neoplasms. It is involved in the formation of transport vesicles from the endoplasmic reticulum. Moreover, SEC31A is involved in gene fusions with at least two gene fusion partners. These include *PTEN* (SEC31A-PTEN) and *ALK* (SEC31A-ALK). SEC31A-ALK fusion has been reported in a patient with recurrent pRCC and observed in lung metastases and many other pRCC studies. **Conclusions:** This is the first study to evaluate OS for pRCC tumor in correlation with gene expression profiles. This study highlights the importance of studying the association of molecular profiles with real-world clinical data and its collection, in understanding pRCC. Research Sponsor: None.

Impact of obesity on immune-related adverse events and tyrosine kinase inhibitor side effects in patients with metastatic renal cell carcinoma (mRCC).

Malak Alharbi, Muhammad Junaid Tariq, Karan Jatwani, Saby George; Roswell Park Cancer Institute, Buffalo, NY; Roswell Park Cancer Institute, Buffalo, IL; Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: A pooled data analysis from clinical trials, including various cancer subtypes, showed that obesity is associated with a heightened incidence of immune-related adverse events (irAEs). However, the heterogeneous patient population across different demographics calls for further investigation into the correlation between obesity and adverse effects from immune checkpoint inhibitors (ICI) in mRCC. Additionally, there is limited available data regarding the association of obesity with tyrosine kinase inhibitors (TKIs) toxicities. We hypothesize that obesity may be linked to an increased rate of irAEs and TKIs toxicities in mRCC patients (pts). **Methods:** We conducted a retrospective analysis of pts diagnosed with mRCC using TriNetX Research Network (TriNetX LLC., Cambridge, Massachusetts, USA). We searched two cohorts (ICI and TKIs) and toxicities using the ICD-10-CM codes. Pts were categorized into two groups based on body mass index (BMI): obese (BMI $\geq$30) and non-obese (BMI >19 - < 30). Characteristics of the cohorts were balanced using propensity score matching. **Results:** A total of 4526 pts with mRCC receiving treatment met the inclusion criteria. 40% of pts were in ICI cohort (n=1811), and 60% (n=2715) in TKI cohort. In the ICI cohort 53% were obese (959/1811), and 47% non-obese (852/1811). Among both cohorts, 50% were male, 30% females, 20% unknown and the average age was 69-72. In TKI cohort, Obese group had 57% (1549/2715) pts while non-obese group included 43% (1166/2715) pts. In ICI cohort, there was no statistically significant difference in risk of developing thyroid dysfunction, liver toxicity, type 1 diabetes, adrenal insufficiency/hypophysitis, skin toxicity, pneumonitis, cardiomyopathy, colitis or myositis/arthropathy between obese and non-obese groups (p>0.05). In TKI cohort, risk of thyroid dysfunction was higher among obese (0.177, n=187/1056) vs non-obese (0.131, n=102/781), p=0.007. Moreover, obese pts had a higher rate of diarrhea compared to non-obese (0.141 vs 0.109, p= 0.017). No significant difference was seen in the rate of developing other toxicities including liver dysfunction, mucositis, cardiovascular toxicities including hypertensive crisis or fatigue. (Table) **Conclusions:** The use of TKIs has shown an increased risk of developing thyroid dysfunction and diarrhea in obese pts. However, there is no difference in irAE with use of ICI between obese and non-obese pts. Further large studies are needed to support this observation and to study the mechanism by which obesity and metabolic syndromes influence the development of adverse effects. Research Sponsor: None.

Adverse Effect	Risk in Obese Group	Risk in Non-Obese Group	p value
Thyroid dysfunction	0.177	0.131	**0.007**
Fatigue	0.141	0.140	0.952
Cardiac toxicity	0.041	0.036	0.516
Mucositis	0.022	0.025	0.618
Diarrhea	0.144	0.109	**0.017**
Liver dysfunction	0.025	0.025	0.955

Treatment outcomes of brain metastasis from primary renal cell carcinoma in United States: A National Cancer Database analysis.

Vivek Podder, Mohammad Arfat Ganiyani, Shahzaib Ahmad, Shreyas S Bellur, Muhammad Abbas Khokhar, Fathima Shehnaz Ayoobkhan, Manas Pustake, Diya K Jayram, Ahmad Ozair, Tulika Ranjan, Rohan Garje, Manmeet Singh Ahluwalia; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; King Edward Medical University, Lahore, Pakistan; Trinity Health Oakland Hospital/Wayne State University, Pontiac, MI; Grant Government Medical College, Mumbai, India; John Hopkins University, Baltimore, MD

Background: The advent of stereotactic radiosurgery (SRS) in treatment of brain metastasis (BM) has improved both clinical outcomes and survival in patients with BM. Recent studies suggest that immunotherapy presents a promising potential in the treatment of patients with BM. However, data regarding the effectiveness of combining SRS with immunotherapy for BM in metastatic renal cell carcinoma (RCC) remain largely unknown. We aim to delineate the impact of various treatment therapies including combination therapy for treatment of RCCBM. **Methods:** We queried the National Cancer Database (NCDB) to include patients with BM from mRCC from 2004 to 2020. We divided the patients into groups based on the treatment they received. Resultantly, 5 different treatment groups i.e., WRBT± immunotherapy, SRS± immunotherapy and immunotherapy alone were identified. We excluded patients with unknown treatment status. We analyzed survival outcomes using the Kaplan-Meier analysis and compared the effect of treatment modalities on survival with the log-rank test. **Results:** The NCDB yielded 6,446 patients diagnosed with BM from mRCC. In eligible cases, the median age was 63 years (range: 19-90+ years), 69.2% were male, 86.8% were White, 7.9% were Black, 41.9% had Medicare as primary payor, 27.7% had annual income >$74,063, 79.3% belonged from metropolitan areas, 39.6% were treated at academic/research program, 68.3% had Charlson-Deyo score of 0, 44.6% had an unknown grade of the primary RCC. 1,705 (43.44%) patients who were given WBRT had a median overall survival (OS) of 5.65 months, 427 (10.88%) patients were treated with SRT + immunotherapy had an OS of 19.0 months, 987 (25.15%) patients who underwent SRT only had an OS of 9.7 months, 431 (10.98%) patients who received immunotherapy only showed an OS of 12.9 months, and 375 (9.55%) patients who underwent WBRT + immunotherapy had an OS of 12.78 months (log-rank p <0.001). **Conclusions:** This national database analysis reveals that the combination of SRS with immunotherapy significantly increases the OS in RCCBM compared to immunotherapy, WBRT, or combination of WRBT and immunotherapy. Further prospective studies are warranted to confirm these findings. Research Sponsor: None.

Difference in patient characteristics among treatment approaches.

Characteristics	WBRT Alone	SRS + Immunotherapy	SRS	Immunotherapy Only	WBRT + Immunotherapy	P value
Age	996	280	533	271	231	<0.0001
≤64						
≥65	754	150	477	164	145	
Facility	641	183	457	166	150	0.0002
Academic						
Others	1109	247	533	269	226	
Insurance	687	217	395	206	155	0.0001
Private						
Medicaid	182	44	1-5	45	42	
Medicare	711	148	440	158	154	
Race	1516	291	889	378	326	0.4312
White						
Black	141	20	66	37	29	

Enfortumab vedotin (EV) with pembrolizumab (P) versus chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC): Analysis of cisplatin (cis)-eligible population from EV-302/KEYNOTE-A39.

Jens Bedke, Michiel Simon Van Der Heijden, Thomas Powles, Begoña Pérez Valderrama, Eiji Kikuchi, Gopa Iyer, Christof Vulsteke, Umang Swami, Daniel Castellano, Naveed Sarwar, Alexandra Drakaki, Jean H. Hoffman-Censits, Waddah Arafat, Timur Andabekov, Jian-Ri Li, Yi-Tsung Lu, Xuesong Yu, Aditya Shetty, Blanca Homet Moreno, Shilpa Gupta; Department of Urology and Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; Netherlands Cancer Institute, Amsterdam, Netherlands; Barts Cancer Centre, QMUL, London, United Kingdom; Hospital Universitario Virgen del Rocío, Seville, Spain; St. Marianna University School of Medicine, Kanagawa, Japan; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Integrated Cancer Center Ghent, AZ Maria Middelares, Ghent and Center for Oncological Research (CORE), Integrated Personalised and Precision Oncology Network (IPPON), University of Antwerp, Antwerp, Belgium; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Hospital Universitario 12 de Octubre, Madrid, Spain; Charing Cross Hospital, London, United Kingdom; University of California, Los Angeles Medical Center, Los Angeles, CA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Greenberg Bladder Cancer Institute; Department of Urology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD; Simmons Comprehensive Cancer Center at University of Texas Southwestern, Dallas, TX; AV Medical Group, Saint-Petersburg, Russian Federation; Taichung Veterans General Hospital, Taichung City, Taiwan; Pfizer Inc., Bothell, WA; Astellas Pharma, Inc., Northbrook, IL; Merck & Co., Inc., Rahway, NJ; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: EV-302/KEYNOTE-A39 (NCT04223856) is a phase 3, randomized, open-label, global study comparing EV+P with platinum-based chemo (PBC) for first-line (1L) treatment (tx) of patients (pts) with la/mUC regardless of cis eligibility. In EV-302, EV+P demonstrated a statistically significant and clinically meaningful benefit compared with PBC for the dual primary endpoints of progression-free survival (PFS) (hazard ratio [HR]: 0.45; P<0.00001) and overall survival (OS) (HR: 0.47; P<0.00001) in the overall pt population (Powles ESMO 2023), reducing the risk of progression and/or death by more than 50%. EV+P was FDA-approved in Dec 2023 for tx of adults with la/mUC. As cis eligibility status has long defined 1L tx, here we present results for pts who were eligible for cis at randomization. **Methods:** Pts with previously untreated la/mUC were randomized 1:1 to receive 3-week cycles of EV (1.25 mg/kg IV; Days 1 and 8) and P (200 mg IV; Day 1) or PBC (gemcitabine with cis or carboplatin). Select secondary endpoints included confirmed objective response rate (ORR), duration of response (DOR), and safety. Pts were deemed eligible/ineligible for cis by protocol-defined criteria and were stratified accordingly. **Results:** 478 pts (EV+P: 244, PBC: 234) were cis-eligible at randomization. 220 (94.0%) pts in the PBC arm received cis at Cycle 1. mPFS was 14.6 mo for EV+P; 6.5 mo for PBC (HR: 0.48, 95% CI, 0.38, 0.62). mOS was 31.5 mo for EV+P; 18.4 mo for PBC (HR: 0.53, 95% CI, 0.39, 0.72). ORR for EV+P was 70.8% with 32.5% complete response (CR) rate; mDOR (95% CI) was not reached (18.2 mo, NR). ORR for PBC was 53.0% with 15.5% CR rate; mDOR (95% CI) was 8.3 mo (5.9, 10.9). In EV+P arm, 82 pts (33.6%) remained on tx at data cutoff (DCO). 85 pts (34.8%) received subsequent therapy. 72 pts (29.5%) received any platinum-based therapy as first subsequent therapy; 43 pts (17.6%) received cis. In PBC arm, all pts were off study tx at DCO. 146 pts (62.4%) received any PD-1/L1 therapy following PBC. 83 pts received maintenance avelumab; 59 pts received PD-1/L1 therapy as 2L tx. Grade ≥3 TRAEs occurred in 53.9% of pts with EV+P and 62.7% of pts with PBC. Most common grade ≥3 TRAEs of special interest for EV were skin reactions (14.8%), hyperglycemia (7.8%), and peripheral neuropathy (5.8%). Most common grade ≥3 tx-emergent AEs of special interest for P were severe skin reactions (9.5%), pneumonitis (4.9%), and colitis (2.9%). **Conclusions:** EV+P improved clinical outcomes in pts who were eligible for cis with previously untreated la/mUC, reducing the risk of death by 47% compared with PBC. Results were consistent with the overall population. The AE profile of EV+P was generally manageable with no new safety signals. The results of EV-302 support EV+P as a new SOC for la/mUC, including pts who are eligible for cis. Clinical trial information: NCT04223856. Research Sponsor: Funded by Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in Dec. 2023; Astellas Pharma, Northbrook, IL; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Enfortumab vedotin (EV) with pembrolizumab (P) versus chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC): Analysis of the cisplatin (cis)-ineligible population from EV-302/KEYNOTE-A39.

Michiel Simon Van Der Heijden, Shilpa Gupta, Jens Bedke, Begoña Pérez Valderrama, Eiji Kikuchi, Gopa Iyer, Yohann Loriot, Nancy Ann Dawson, Jean H. Hoffman-Censits, Nataliya Mar, Srikala S. Sridhar, Pablo Maroto-Rey, Sang Joon Shin, Evan Y. Yu, Ignacio Duran, Matthew Birrenkott, Xuesong Yu, Aditya Shetty, Abhishek Amar Bavle, Thomas Powles; Netherlands Cancer Institute, Amsterdam, Netherlands; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Department of Urology and Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; Hospital Universitario Virgen del Rocío, Seville, Spain; St. Marianna University School of Medicine, Kanagawa, Japan; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Université Paris-Sud, Université Paris-Saclay, Gustave Roussy, Villejuif, France; Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Greenberg Bladder Cancer Institute; Department of Urology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD; University of California, Irvine Medical Center, Orange, CA; Princess Margaret Cancer Centre, Toronto, ON, Canada; Santa Creu i Sant Pau Hospital, Barcelona, Spain; Severance Hospital Yonsei University Health System, Seoul, South Korea; Seattle Cancer Care Alliance/University of Washington, Seattle, WA; Department of Medical Oncology, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; Pfizer Inc., Bothell, WA; Astellas Pharma, Inc., Northbrook, IL; Merck & Co., Inc., Rahway, NJ; Barts Cancer Centre, QMUL, London, United Kingdom

Background: EV-302/KEYNOTE-A39 (NCT04223856) is a phase 3, randomized, open-label, global study comparing EV+P with platinum-based chemo (PBC) for first-line (1L) treatment (tx) of patients (pts) with la/mUC regardless of cis eligibility. In EV-302, EV+P demonstrated a statistically significant and clinically meaningful benefit compared with PBC for the dual primary endpoints of PFS (hazard ratio [HR]: 0.45; P<0.00001) and OS (HR: 0.47; P<0.00001) in the overall pt population (Powles ESMO 2023), reducing the risk of progression and/or death by more than 50%. EV+P was FDA-approved in Dec 2023 for tx of adults with la/mUC. As cis eligibility status has long defined 1L tx, here we present results of an analysis for pts who were ineligible for cis at randomization. **Methods:** Pts with previously untreated la/mUC were randomized 1:1 to receive 3-week cycles of EV (1.25 mg/kg IV; Days 1 and 8) and P (200 mg IV; Day 1) or PBC (gemcitabine with cis or carboplatin [carbo]). Select secondary endpoints included confirmed objective response rate (ORR), duration of response (DOR), and safety. Pts were deemed eligible/ineligible for cis following protocol-defined criteria and stratified accordingly. **Results:** 408 pts (EV+P: 198, PBC: 210) were cis-ineligible at randomization. 205 (97.6%) pts in the PBC arm received carbo at Cyle 1. mPFS was 10.6 months for EV+P; 6.1 months for PBC (HR: 0.43, 95% CI, 0.33, 0.55). mOS was not reached for EV+P and was 12.7 months for PBC (HR: 0.43, 95% CI, 0.31, 0.59). ORR for EV+P was 63.9% with 24.7% complete response (CR) rate; mDOR (95% CI) was not reached (16.3 months, NR). ORR for PBC was 34.9% with 9.1% CR rate; mDOR (95% CI) was 6.6 months (5.6, 10.2). In EV+P arm, 62 pts (31.3%) remained on tx at data cutoff (DCO). 55 pts (27.8%) received subsequent therapy. 10 pts received cis and 27 pts received carbo as first subsequent therapy. In PBC arm, all were off study tx at DCO. 114 pts (54.3%) received any PD-1/L1 therapy following PBC. 52 pts received maintenance avelumab; 58 pts received PD-1/L1 therapy as second-line tx. Grade ≥3 TRAEs occurred in 58.4% of pts with EV+P and 77.1% of pts with PBC. Most common grade ≥3 TRAEs of special interest for EV were skin reactions (16.2%), peripheral neuropathy (8.1%), and hyperglycemia (4.1%). Most common grade ≥3 tx-emergent AEs of special interest for P were severe skin reaction (14.7%), hepatitis (2.0%), and pneumonitis (2.0%). **Conclusions:** In this pt population with historically poor prognosis, EV+P improved clinical outcomes in pts who were ineligible for cis; results were consistent with the overall population. The risk of death was reduced by more than 50%. The AE profile of EV+P was generally manageable with no new safety signals. The results of EV-302 support EV+P as a new SOC for la/mUC, including pts who are ineligible for cis. Clinical trial information: NCT04223856. Research Sponsor: Funded by Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in Dec. 2023; Astellas Pharma, Northbrook, IL; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Study EV-103: Neoadjuvant treatment with enfortumab vedotin monotherapy in cisplatin-ineligible patients with muscle invasive bladder cancer (MIBC)—2-year event-free survival and safety data for Cohort H.

Peter H. O'Donnell, Christopher J. Hoimes, Jonathan E. Rosenberg, Daniel P. Petrylak, Nataliya Mar, Pedro C. Barata, Sandy Srinivas, Theodore Stewart Gourdin, Elizabeth Henry, Mehmet Asim Bilen, Saby George, Santosh Rao, Vasileios J. Assikis, Earle F Burgess, Brian E. Lewis, I. Alex Bowman, Sam Joseph Brancato, Shirly Mildiner-Earley, Yalin Zhu, Thomas W. Flaig; University of Chicago, Chicago, IL; Duke Cancer Institute, Duke University, Durham, NC; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Yale Cancer Center, Yale School of Medicine, New Haven, CT; University of California, Irvine Medical Center, Orange, CA; University Hospitals Seidman Cancer Center, Cleveland, OH; Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA; Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; Loyola University, Chicago, IL; Winship Cancer Institute of Emory University, Atlanta, GA; Roswell Park Comprehensive Cancer Center, Buffalo, NY; University Hospitals Case Medical Center, Cleveland, OH; Piedmont Cancer Institute, P.C., Atlanta, GA; Levine Cancer Institute, Charlotte, NC; Tulane University, New Orleans, LA; Banner MD Anderson Cancer Center, Gilbert, AZ; Astellas Pharma Inc., Northbrook, IL; Pfizer Inc., San Francisco, CA; Pfizer Inc., Bothell, WA; University of Colorado Anschutz Medical Campus, Aurora, CO

Background: For patients (pts) with MIBC who are cisplatin-ineligible and undergoing radical cystectomy and pelvic lymph node dissection (RC+PLND), no neoadjuvant treatment options have been shown to improve survival. Enfortumab vedotin (EV) is an antibody-drug conjugate directed to Nectin-4, which is highly expressed in urothelial cancer. EV, alone and in combination w/ pembrolizumab, has been shown to improve OS vs chemotherapy in pts with previously treated and untreated locally advanced or metastatic urothelial cancer, respectively (Powles NEJM 2021; Powles ESMO 2023). In Cohort H of the EV-103 phase 1b/2 study, promising results for 1-year EFS and antitumor activity, including pathological complete response (pCR) and pathological downstaging (pDS) rates, were achieved in cisplatin-ineligible pts with MIBC after neoadjuvant monotherapy EV treatment (Petrylak ASCO GU 2022; Flaig ASCO 2023). Here we report updated results, including 2-year EFS. **Methods:** Cohort H of the EV-103 study enrolled cisplatin-ineligible pts with MIBC (T2-T4aN0M0) and ECOG PS ≤2 who were eligible for RC+PLND. Pts received neoadjuvant EV (1.25 mg/kg) on Days 1 and 8 every 21 days for 3 cycles before undergoing RC+PLND. The primary endpoint was pCR rate (ypT0 and N0) by central pathology review. Key secondary endpoints included pDS rate (ypT0, ypTis, ypTa, ypT1, and N0), safety, and EFS per investigator assessment (radiographic progression prior to RC, failure to undergo RC, gross residual disease at time of RC, recurrence, or death). **Results:** 22 pts (median age 74.5 years) were enrolled and treated; 15 pts (68.2%) remain on study. Pts had stage cT2 (68.2%), cT3 (27.3%), or cT4 (4.5%) disease. 68.2% of pts had urothelial carcinoma only; 31.8% had a mixed histology. 86.4% of pts completed all 3 cycles of EV; the median duration of EV treatment was 2.1 months (range 0.7-2.3). The pCR rate was 36.4% (95% CI, 17.2-59.3) and the pDS rate was 50.0% (95% CI, 28.2-71.8). The EFS rate at 24 months was 62.0% (95% CI, 38.2-78.9). Median EFS has not been reached. All pts underwent surgery with no delays due to EV-related TEAEs. The most common EV-related TEAEs were fatigue (45.5%), dysgeusia (36.4%), and alopecia (31.8%); 18.2% of pts had grade ≥3 EV-related TEAEs. 68.2% of pts had surgery-related TEAEs: the most common were procedural pain (18.2%), anemia (13.6%), and constipation (13.6%). 3 pts died due to AEs unrelated to EV treatment. 36.4% of pts received subsequent cancer-related therapy. **Conclusions:** Neoadjuvant EV monotherapy treatment showed promising results for antitumor activity and 2-year EFS with a manageable safety profile in cisplatin-ineligible pts with MIBC. These results support ongoing phase 2 and 3 programs in MIBC evaluating EV alone or combined with pembrolizumab (EV-103 Cohort L, KN-905/EV-303, KN-B15/EV-304). Clinical trial information: NCT03288545. Research Sponsor: Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in Dec. 2023; Astellas Pharma, Northbrook, IL.

Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: Results from the bladder cohort of the DESTINY-PanTumor02 (DP-02) study.

Piotr Jan Wysocki, Kyung Hae Jung, Do-Youn Oh, Deborah Blythe Doroshow, Elena Artamonova, Lemonitsa Mammatas, Po-Jung SU, Vladimir Moiseyenko, Konstantin Penkov, Daniil Stroyakovskiy, Jorge Bartolome, Salvatore Siena, Anitra Fielding, Lindsey Jung, Flavia Michelini, Soham D. Puvvada, Vicky Makker; Jagiellonian University Medical College Hospital, Kraków, Poland; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Seoul National University Hospital, Seoul, South Korea; Icahn School of Medicine at Mount Sinai, New York, NY; N.N Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation; Reinier de Graaf Gasthuis, Delft, Netherlands; Linkou Chang Gung Memorial Hospital, Taoyuan City, Taiwan; Saint Petersburg Clinical Research Center of Specialized Types of Medical Care (Oncology) Named After N.P Napalkov, Saint Petersburg, Russian Federation; Clinical Hospital "RZHD-Medicine", St. Petersburg, Russian Federation; Moscow City Oncology Hospital No. 62, Moscow, Russian Federation; Hospital Clínico San Carlos, Madrid, Spain; Università degli Studi di Milano and Niguarda Cancer Center, Milan, Italy; AstraZeneca, Gaithersburg, MD; Translational Medicine, Oncology R&D, AstraZeneca, Waltham, MA; Oncology R&D, AstraZeneca, Gaithersburg, MD; Memorial Sloan Kettering Cancer Center, New York, NY

Background: In DP-02, T-DXd showed robust responses and clinically meaningful survival outcomes in 267 pretreated pts with HER2-expressing solid tumors; the objective response rate (ORR) by investigator (INV) was 37.1% (95% CI 31.3, 43.2). Here we report subgroup analyses in the bladder cohort (urothelial carcinoma including transitional cell carcinoma of the renal pelvis, ureter, urinary bladder, or urethra), and characterize pts with an objective response (OR). **Methods:** This open-label, Phase 2 study (NCT04482309) evaluated T-DXd (5.4 mg/kg Q3W) in pts with HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing) locally advanced/metastatic disease after ≥1 systemic treatment (Tx), or without Tx options. The primary endpoint was confirmed ORR by INV. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and safety. Exploratory endpoints included efficacy outcomes according to HER2 expression. **Results:** At data cutoff (June 2023), 41 pts with urothelial cancers had received T-DXd (median [m] follow up [range]: 12.65 [0.4–26.8] months); 27 (65.9%) had received ≥2 prior Tx regimens. 16/41 pts (39.0%; 95% CI 24.2, 55.5) had a confirmed OR by INV; 12 responders had received ≥2 prior Tx regimens, 14 had received prior immunotherapy Tx, and 14 had known PD-L1 immune cell status ≥1%. The Table shows efficacy outcomes in all pts and by HER2 expression (central testing). Grade (G) ≥3 drug-related adverse events occurred in 17/41 (41.5%) pts. Adjudicated drug-related interstitial lung disease / pneumonitis occurred in 4/41 (9.8%) pts (n=1 G1; n=3 G2). **Conclusions:** T-DXd showed clinically meaningful responses in pretreated pts with urothelial cancers, including across HER2 expression levels (IHC 3+ and 2+). Safety was consistent with the known profile. These data support further evaluation of T-DXd as a potential Tx for pretreated pts with HER2-expressing urothelial cancers. Clinical trial information: NCT04482309. Research Sponsor: This study is sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

	All Pts	HER2 IHC 3+	HER2 IHC 2+	HER2 IHC 1+	HER2 IHC 0
n	41	16	20	2	2
Pts with OR, n	16	9	7	0	0
ORR, % (95% CI)	39.0 (24.2, 55.5)	56.3 (29.9, 80.2)	35.0 (15.4, 59.2)	0	0
mDOR, months (95% CI)	8.7 (4.3, 11.8)	8.7 (2.8, 10.6)	10.3 (4.3, 17.8)	-	-
mPFS, months (95% CI)	7.0 (4.2, 9.7)	7.4 (3.0, 11.9)	7.8 (2.6, 11.6)	5.5 (4.0, NE)	2.6 (1.0, NE)
DCR at 12 weeks, % (95% CI)	70.7 (54.5, 83.9)	75.0 (47.6, 92.7)	70.0 (45.7, 88.1)	100 (15.8, 100)	50.0 (1.3, 98.7)

By INV. Local HER2 status confirmed by central testing; upon reanalysis, some pts were IHC 1+/0/unknown. 1 pt: central IHC unknown. DOR was assessed in pts with an OR. CIs omitted: 0%. NE, not evaluable.

Avelumab first-line maintenance (1LM) for advanced urothelial carcinoma (aUC): Long-term outcomes from JAVELIN Bladder 100 in patients (pts) with low tumor burden.

Joaquim Bellmunt, Thomas Powles, Se Hoon Park, Eric Voog, Begoña Pérez Valderrama, Howard Gurney, Anders Ullén, Yohann Loriot, Srikala S. Sridhar, Norihiko Tsuchiya, Cora N. Sternberg, Jeanny B. Aragon-Ching, Daniel P. Petrylak, Miguel A. Climent Duran, Karin Tyroller, Jason Hoffman, Natalia Jacob, Petros Grivas, Shilpa Gupta; Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, MA; Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, United Kingdom; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Clinique Victor Hugo, Centre Jean Bernard, Le Mans, France; Hospital Universitario Virgen del Rocío, Seville, Spain; Department of Clinical Medicine, Macquarie University, Westmead, Australia; Karolinska University Hospital, Solna, Sweden; Gustave Roussy, INSERMU981, Université Paris-Saclay, Villejuif, France; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Yamagata University Faculty of Medicine, Yamagata, Japan; Englander Institute for Precision Medicine, Meyer Cancer Center, New York, NY; Inova Schar Cancer Institute, Fairfax, VA; Yale Cancer Center, New Haven, CT; Instituto Valenciano de Oncología, Valencia, Spain; EMD Serono, Billerica, MA; The Healthcare Business of Merck KGaA, Darmstadt, Germany; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: In the JAVELIN Bladder 100 phase 3 trial, avelumab 1LM + best supportive care (BSC) significantly prolonged overall survival (OS) and progression-free survival (PFS) vs BSC alone in pts with aUC that had not progressed with 1L platinum-based chemotherapy (PBC). Results led to the incorporation of avelumab 1LM into international guidelines. Prior analyses have shown that low tumor burden (eg, nonvisceral metastases or lymph node [LN]-only disease) is associated with better outcomes in pts with aUC receiving immune checkpoint inhibitors. We report post hoc analyses of efficacy and safety in subsets of pts with low tumor burden from JAVELIN Bladder 100. **Methods:** Eligible pts with unresectable locally advanced (LA) or metastatic UC without progression after 1L PBC were randomized 1:1 to receive avelumab + BSC (n=350) or BSC alone (n=350). The primary endpoint was OS measured from randomization; secondary endpoints included PFS and safety. In this post hoc analysis, pts with nonvisceral metastases included those with LA disease or only nonvisceral disease, including bone metastasis, at randomization. **Results:** In the avelumab + BSC and BSC alone arms, 159 and 159 pts had nonvisceral metastases and 51 and 51 pts had LN-only disease, of whom 42 and 35 pts had LN-only disease in the pelvic/retroperitoneal area. At the efficacy data cutoff (June 4, 2021), median follow-up was ≥38 mo in both arms (≥2 y in all pts). In all subgroups, OS and PFS were prolonged with avelumab + BSC vs BSC alone (Table). Incidence of treatment-related adverse events (TRAEs) with avelumab were similar across subgroups. In the avelumab + BSC and BSC alone arms, subsequent anticancer drug treatment was received by 90 (56.6%) vs 119 pts (74.8%) with nonvisceral metastases, 27 (52.9%) vs 39 pts (76.5%) with LN-only disease, and 22 (52.4%) vs 27 pts (77.1%) with pelvic/retroperitoneal LN-only disease. **Conclusions:** Exploratory analyses suggest that avelumab 1LM has pronounced efficacy and manageable toxicity in pts with aUC who have low tumor burden, supporting its use as a standard of care in this setting. Clinical trial information: NCT02603432. Research Sponsor: Pfizer; the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	Nonvisceral Metastases		LN-Only Disease		Pelvic/Retroperitoneal LN-Only Disease	
	Avelumab + BSC (n=159)	BSC (n=159)	Avelumab + BSC (n=51)	BSC (n=51)	Avelumab + BSC (n=42)	BSC (n=35)
Median OS,* mo (95% CI)	31.4 (26.1-36.8)	17.1 (13.7-21.3)	31.9 (26.1-44.5)	22.7 (16.5-NE)	31.2 (23.8-44.5)	20.2 (13.7-NE)
Stratified HR for OS (95% CI)	0.60 (0.45-0.79)		0.86 (0.51-1.47)		0.72 (0.39-1.31)	
Median PFS by investigator,* mo (95% CI)	9.0 (5.7-12.6)	3.3 (2.0-3.7)	8.7 (5.4-24.7)	3.7 (2.0-6.0)	7.5 (4.2-12.0)	3.7 (1.9-5.7)
Stratified HR for PFS (95% CI)	0.45 (0.35-0.59)		0.51 (0.31-0.84)		0.44 (0.24-0.79)	
TRAEs, n (%)†						
Any grade	122 (77.2)	2 (1.3)	44 (88.0)	0	36 (87.8)	0
Grade ≥3	30 (19.0)	0	8 (16.0)	0	6 (14.6)	0

NE, not estimable. *Measured from randomization. †Treated pts; data cutoff: April 6, 2023.

Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (aUC): Long-term outcomes from the JAVELIN Bladder 100 trial in patients (pts) with histological subtypes.

Yohann Loriot, Shilpa Gupta, Thomas Powles, Petros Grivas, Daniel P. Petrylak, Karin Tyroller, Natalia Jacob, Jason Hoffman, Joaquim Bellmunt; Gustave Roussy, INSERMU981, Université Paris-Saclay, Villejuif, France; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, United Kingdom; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Yale Cancer Center, New Haven, CT; EMD Serono, Billerica, MA; The Healthcare Business of Merck KGaA, Darmstadt, Germany; Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, MA

Background: Results from the phase 3 JAVELIN Bladder 100 trial (NCT02603432) led international treatment guidelines to recommend avelumab 1L maintenance as a standard-of-care treatment for pts with aUC without progression after 1L platinum-based chemotherapy (PBC). Around 20% of UCs are mixed with other histological subtypes/variants; these tumors do not have specific treatment guidelines and represent an unmet treatment need. In the large real-world AVENANCE study (NCT04822350; N=594) of avelumab 1L maintenance in pts with aUC in France, outcomes in pts with histological subtypes were consistent with those in the overall population. Here, we report a post hoc analysis of long-term outcomes from JAVELIN Bladder 100 in pts with predominantly UC mixed with <50% histological subtype component. **Methods:** Eligible pts had unresectable locally advanced or metastatic UC without progression after 1L PBC and were randomized 1:1 to receive avelumab + best supportive care (BSC) or BSC alone. The primary endpoint was overall survival (OS) measured from randomization; secondary endpoints included progression-free survival (PFS) and safety. This post hoc analysis was conducted in all pts with histological subtypes. **Results:** In the avelumab + BSC and BSC alone arms, respectively, 44/350 and 57/350 pts had histological subtypes. At efficacy data cutoff (June 4, 2021), median follow-up in both arms was ≥38.0 mo. In pts with histological subtypes, OS and PFS measured from randomization were prolonged with avelumab + BSC vs BSC alone (Table). Long-term safety (cutoff, April 6, 2023) in treated pts with histological subtypes was generally consistent with the overall safety population. Treatment-related adverse events (TRAEs) of any grade occurred in 36 pts (83.7%) in the avelumab + BSC arm vs 1 pt (1.8%) in the BSC alone arm; grade ≥3 TRAEs occurred in 9 pts (20.9%) and 0 pts, respectively. **Conclusions:** This exploratory analysis shows the long-term efficacy and safety of avelumab 1L maintenance in pts with histological subtypes in JAVELIN Bladder 100. No new safety concerns were identified. These results were consistent with those in the overall population and support the use of avelumab 1L maintenance in pts with aUC without progression following 1L PBC, including pts with predominantly UC mixed with <50% histological subtype component. Clinical trial information: NCT02603432. Research Sponsor: Pfizer; the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Pts With UC Mixed With Histological Subtypes	Avelumab + BSC (n=44)	BSC (n=57)
Median OS, mo (95% CI)	19.3 (13.6-36.8)	14.1 (9.3-24.3)
2-y OS rate, % (95% CI)	43.0 (28.0-57.2)	40.0 (26.6-53.1)
3-y OS rate, % (95% CI)	37.1 (22.5-51.8)	31.3 (19.0-44.4)
Stratified HR for OS (95% CI)	0.74 (0.44-1.24)	
Median PFS by investigator, mo (95% CI)	4.2 (2.0-7.2)	2.0 (1.9-3.5)
2-y PFS rate, % (95% CI)	19.7 (9.3-32.9)	3.9 (0.7-11.9)
3-y PFS rate, % (95% CI)	19.7 (9.3-32.9)	3.9 (0.7-11.9)
Stratified HR for PFS (95% CI)	0.52 (0.33-0.83)	

4568 Poster Session

Preliminary efficacy and safety results from RC48-C017: A phase II study of neoadjuvant treatment with disitamab vedotin plus toripalimab in patients with muscle invasive bladder cancer (MIBC) with HER2 expression.

Xinan Sheng, Kaiwei Yang, Yongpeng Ji, Li Zhou, Benkui Zou, Hang Huang, Yonghua Wang, Xue Bai, Dan Feng, Yong Yang, Jiasheng Bian, Zhixian Yu, Haitao Niu, Peng Du, Jianmin Fang, Zhisong He, Jun Guo; Department of Genitourinary Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Peking University First Hospital, Department of Urology, Beijing, China; Peking University Cancer Hospital, Department of Urology, Beijing, China; Melanoma Institute Australia, Sydney, Australia; Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong, Jinan, China; The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; The Affiliated Hospital of Qingdao University, Qingdao, China; RemeGen Co., Ltd., Yantai, China; Department of Urology, Peking University Cancer Hospital, Beijing, China; School of Life Science and Technology, Tonji Univesity, Shanghai, China; Peking University First Hospital, Beijing, China; Department of Genitourinary Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Collaborative Innovation Center of Cancer Medicine, Beijing, China

Background: Disitamab vedotin (DV) is a novel humanized anti-HER2 antibody-drug conjugate. DV plus toripalimab (a recombinant humanized anti-PD-1 monoclonal antibody) showed promising antitumor activity in metastatic urothelial carcinoma (ASCO 2023). This study aimed to evaluate the safety and efficacy of DV plus toripalimab as neoadjuvant therapy in MIBC patients with HER2 expression. **Methods:** This is a prospective multicenter phase 2 trial which planned to enroll 40 pts. Primary endpoint is pathological CR (pCR) rate; secondary endpoints include pathologic response rate, safety and tolerability. Study enrolled pts who are previously untreated MIBC (cT2-T4aN0-1M0), medically fit for and agree to undergo curative intent RC+PLND. HER2 expression was required to be immunochemistry (IHC) $\geq$ 1+ tested locally. Pts received DV 2 mg/kg plus toripalimab 3 mg/kg every two weeks for 6 cycles, followed by RC+PLND within 4 weeks. Here we present preliminary efficacy and safety results. **Results:** 44 pts were enrolled and clinical stage at diagnosis was: cT2N0 (38.6%), cT3N0 (29.5%), cT4aN0 (13.6%), cT2-4aN1 (18.2%). HER2 expression of IHC 1+, 2+ or 3+ was 11.4%, 56.8%, and 31.8%, respectively. By the data cut-off date (Feb-2024), 29 pts (65.9%) completed RC + PLND. The pCR rate was 62.1% (18/29). The pathologic response rate was 75.9% (22/29). Common treatment-related adverse events (TRAEs) were mostly Grade 1 or 2, including alopecia (36.4%), alanine aminotransferase increased (31.8%), aspartate aminotransferase increased (25.0%), rash (22.7%), gamma-glutamyl transferase increased (22.7%), peripheral sensory neuropathy (22.7%), and asthenia (20.5%). Grade 3-4 TRAEs were reported in 15.9% of pts. No deaths occurred. No surgery was cancelled due to TRAEs. Survival data are not yet mature. **Conclusions:** Neoadjuvant treatment with DV plus toripalimab showed promising efficacy results and was well tolerated in operable MIBC pts with HER2 expression. These results will support further investigation for DV plus toripalimab in this population. Clinical trial information: NCT05297552. Research Sponsor: RemeGen Co., Ltd., Beijing, China.

Correlation of peripheral blood monocytic myeloid-derived suppressor cells (M-MDSC) and T-cell receptor (TCR) dynamics with clinical outcomes in patients (pts) with metastatic urothelial carcinoma (mUC) treated with nivolumab (NIVO).

Aditi Gupta, Karissa Whiting, Niamh M. Keegan, Joe Schmalz, Hikmat A. Al-Ahmadie, Ashley M. Regazzi, Asia S. McCoy, Colleen Anne Maher, Gopa Iyer, Jonathan E. Rosenberg, Phillip Wong, Teresa Ho, Irina Ostrovnaya, Margaret K. Callahan, Samuel A Funt; Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Adaptive, Seattle, WA; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: Although PD-1 blockade is active in varied mUC treatment settings, predicting response and overcoming resistance remain unmet needs. We hypothesized that immunosuppressive M-MDSCs ($CD14^{+}Lin^{-}/HLA\text{-}DR^{low/-}$) and TCR dynamics in tumors and blood may correlate with outcomes from NIVO in pts with platinum-refractory mUC (NCT02553642). **Methods:** 69 pts with mUC were treated with NIVO 240mg intravenously every 2 weeks (wks). Pre-treatment peripheral M-MDSCs among lineage-negative CD14+ monocytes (%) were estimated by flow cytometry using an algorithm that calculates MDSC frequencies based on HLA-DR mean fluorescence intensity (Kitano et al. 2014). High throughput DNA sequencing of the CDR3 region of the TCR beta chain was performed on baseline tumors (N = 57) and pre and post-treatment (wk 2) peripheral blood mononuclear cells using Adaptive Immunosequencing (Adaptive Biotechnologies). M-MDSC levels and TCR metrics were correlated with clinical outcomes: complete or partial response (CR, PR) vs. stable or progressive disease (SD, PD) by RECIST 1.1, clinical benefit (CR + PR + SD), and progression-free and overall survival (PFS, OS). Groups were compared using Wilcoxon signed rank (paired), Wilcoxon rank sum tests (unpaired), and log-rank tests (time-to-event). Cox proportional hazards and logistic regression models were used to analyze binary and time-to-event outcomes, respectively. **Results:** Higher pre-treatment M-MDSCs were associated with worse PFS and OS univariably (PFS HR 1.07; 95% CI, 1.01-1.14; p = 0.025; OS HR 1.07; 95% CI, 1.00-1.14; p = 0.038), and after adjustment for liver disease and PD-L1 at baseline (PFS HR 1.12; 95% CI, 1.04-1.21, p = 0.004; OS HR 1.11; 95% CI, 1.03-1.20, p = 0.010). Baseline M-MDSCs did not significantly differ between responders and non-responders, but were significantly lower in patients with clinical benefit (median 12.8 [IQR: 10.7-15.9] vs. median 15.6 [IQR: 13.5-18.3]; p = 0.039), and remained significantly associated after adjustment for PD-L1 score in a multivariable model (OR 0.82; 95% CI, 0.67-0.97; p = 0.037). A higher number of tumor-associated clones in the blood (BTACs) at baseline was associated with response (p = 0.049). Overall, BTACs significantly increased at wk 2 ($p < 0.001$), and wk 2 values were associated with response (p = 0.003). PFS also significantly differed between BTAC high (high: > median 2,012 clones) and low groups at wk 2, with improved PFS in the high group (log-rank p = 0.026). OS rate for the BTAC high group was 34% vs. 16% for the low group at wk 2, but this did not achieve significance (p = 0.098). **Conclusions:** Peripheral M-MDSCs may promote resistance to PD-1 blockade in pts with mUC. NIVO stimulated tumor-specific TCR clones in the blood, which correlated with improved response and outcomes. Clinical trial information: NCT02553642. Research Sponsor: None.

Age and other criteria influencing nontreatment of patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC): Results of a physician survey in five European countries (Eu5).

Shilpa Gupta, Thomas Powles, Mairead Kearney, Laura Panattoni, Natalie Land, Thomas Flottemesch, Patrick Sullivan, Melissa Kirker, Murtuza Bharmal, Silke Guenther, Nuno Costa, Enrique Grande; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, United Kingdom; The Healthcare Business of Merck KGaA, Darmstadt, Germany; Precision Value and Health, New York, NY; Nova Southeastern College of Pharmacy, New York, NY; Pfizer Inc., New York, NY; EMD Serono, Rockland, MA; Pfizer, Porto Salvo, Portugal; Medical Oncology Department, MD Anderson Cancer Center Madrid, Madrid, Spain

Background: Real-world studies have shown that a majority of pts with la/mUC do not receive first-line (1L) systemic therapy (tx), despite guideline recommendations. This cross-sectional study assessed the criteria that Eu5 physicians consider when making decisions about 1L tx for pts with la/mUC. **Methods:** A quantitative online survey of Eu5 physicians was performed in Aug-Sep 2022. Respondents answered questions related to demographics, practice patterns, and criteria considered in 1L decision-making. Descriptive statistics were used to analyze demographics and responses. Logistic regression was used to analyze physician characteristics associated with reporting no age threshold vs any age threshold when defining platinum ineligibility. **Results:** 503 physicians (69% oncologists and 31% urologists) completed the quota-based survey. Most respondents had been in practice for >10 years (69%) and treated 5-19 pts with la/mUC per month (58%) in public teaching hospitals (40%), public nonteaching hospitals (24%), and private hospitals (20%). Physicians estimated that they do not prescribe 1L tx for ≈25% of their pts. The majority of physicians selected advanced age (62.0%) and poor performance status (PS; 54.7%) as their top reasons for not prescribing 1L tx, followed by pt refusal (45.9%) and poor renal function (43.1%). Most physicians (78.1%) reported having an age threshold above which they recommend against 1L systemic tx (mean, 74.7 years old [Table]). After adjusting for baseline characteristics, physicians were more likely to have an age threshold if they were from Italy vs Germany (odds ratio [OR] 0.22 [95% CI 0.06-0.73]), practiced in a public nonteaching hospital (OR 0.28 [95% CI 0.10-0.73]) or public/private office settings (OR 0.14 [95% CI 0.03-0.57]) vs private hospital, and if they treated <20 pts/month (2-10 pts: OR 0.36 [95% CI, 0.17-0.74]; 11-19 pts: OR 0.25 [95% CI 0.09-0.62]). **Conclusions:** 1L systemic tx rates self-reported by Eu5 physicians were higher than those previously published. Many physicians reported having an age threshold for not offering systemic tx, which was relatively low compared with the senior age profile of the la/mUC population. Physicians who reported an explicit age threshold may be inappropriately excluding pts from tx; this could be a driver for systemic tx underutilization in la/mUC. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945); Pfizer.

	Full Sample (N=503)	Germany (n=101)	Spain (n=102)	France (n=100)	Italy (n=100)	UK (n=100)
Proportion of pts not treated with any systemic tx as reported by physicians, mean, % (SD)	25.0 (18.5)	25.7 (17.4)	26 (18.6)	23.1 (18.6)	25.2 (13.6)	25.1 (19.4)
Physicians reporting an age threshold to recommend against 1L systemic tx, %	78.1	73.3	78.4	74.4	91.0	74.0
Age threshold reported by physicians, mean (SD), years	74.7 (13.7)	75.7 (13.7)	77.3 (12.6)	66.6 (18.1)	75.1 (10.9)	78.7 (9.2)

Associations of dietary fructose with survival of patients (pts) with metastatic cancer of the urothelium (UC) and renal cell carcinoma (RCC) on immune checkpoint blockade (ICB).

Anas Badri, Brendan John Guercio, Neha Ratna, David Gavrilov, Nicholina Metzker, Cihan Duzgol, Min Yuen Teo, Ashley M. Regazzi, Lauren Supplice, Samuel A Funt, David H Aggen, Martin H Voss, Marie Isabel Carlo, Neil J. Shah, Robert J. Motzer, Dean F. Bajorin, Jonathan E. Rosenberg, Chung-Han Lee, Ritesh R Kotecha, Gopa Iyer; James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Memorial Sloan Kettering Cancer Center and Exelixis, New York, NY

Background: The gut microbiome is a modifiable determinant of ICB efficacy. Dietary fiber is associated with longer progression-free survival (PFS) on ICB in melanoma and UC, putatively via effects on the gut microbiome. Other dietary factors may also impact ICB efficacy. Fructose promotes adverse health effects and induces ICB resistance in pre-clinical models via upregulation of the antiapoptotic enzyme heme oxygenase-1. Thus, we set out to explore effects of fructose intake on ICB efficacy. **Methods:** In a retrospective analysis of a prospectively collected cohort, we leveraged dietary data collected with the validated Harvard Willett Food Frequency Questionnaire from pts with advanced UC and RCC initiating ICB at Memorial Sloan Kettering to assess for associations between baseline dietary fructose and PFS and overall survival (OS). Tumor mutational burden (TMB) was estimated via MSK-IMPACT. Associations of fructose with clinical outcomes were evaluated using univariate (UV) and multivariable (MV) Cox proportional hazards regression. Fructose was normalized via log transformation and treated as a continuous variable. MV models adjusted for fiber intake and prior ICB exposure. UC models adjusted for TMB and Bellmunt risk score and RCC models for histology and IMDC score. **Results:** From 2/2021-6/2022, 88 eligible pts enrolled. Median follow-up was 10.2 and 17.0 months among pts with UC (n = 40) and RCC (n = 48), respectively; 32 RCC pts (67%) were IMDC intermediate/poor risk and 21 UC pts (52%) had visceral metastases. High fructose and fiber intake correlated (rho 0.66). Among UC pts, higher fructose was associated with shorter PFS after adjusting for covariables (Table). In the MV model, high fiber was associated with longer PFS (HR 0.2, 95% CI 0.07-0.62, p = .004). Among RCC pts, fructose was not associated with PFS. Fructose was associated with OS in the RCC UV model, but this association was not statistically significant in the MV model (Table). In an exploratory model for PFS pooling all pts, a test for interaction between fructose intake and disease type (UC vs RCC) showed p = .01. **Conclusions:** Dietary fructose is associated with shorter PFS in UC pts treated with ICB, but not RCC pts. Discrepant results between UC and RCC require further study and may be attributable to differences in therapy or cancer biology. Our findings provide insights into potentially beneficial dietary interventions. Efforts to characterize effects of fructose on the gut microbiome are ongoing. Research Sponsor: Bladder Cancer Advocacy Network; Kidney Cancer Association; National Cancer Institute/U.S. National Institutes of Health; P50-CA221745; National Cancer Institute/U.S. National Institutes of Health; P30-CA008748.

Hazard ratios for outcomes by dietary fructose intake.

	UC (n = 40)		RCC (n = 48)	
Fructose intake (g/d), median (IQR)	15 (12-32)		19 (12-22)	
Outcome	HR (95% CI)	p	HR (95% CI)	p
UV PFS	1.59 (0.87-2.91)	0.13	0.43 (0.19-1.01)	0.05
MV PFS	3.94 (1.57-9.90)	**0.004**	0.52 (0.16-1.70)	0.28
UV OS	1.86 (0.80-4.34)	0.15	0.26 (0.08-0.83)	**0.02**
MV OS	3.00 (0.78-11.47)	0.11	0.87 (0.10-7.4)	0.90

Analyzing disparities in socioeconomic factors, clinical characteristics, and outcomes in bladder cancer: Insights from the National Cancer Database (NCDB).

Faran Polani, Min Woo Hwang, Eun-mi Yu, Hongkun Wang, Jeanny B. Aragon-Ching; Inova Schar Cancer Institute, Fairfax, VA; Department of Biostatistics, Bioinformatics and Biomathematics, Georgetown University, Washington, DC

Background: Social determinants of health can influence mortality in bladder cancer. We sought to understand the trends and survival differences for urothelial cancer (UC) and non-urothelial cancer (nUC) based on demographic, socioeconomic, clinical, and treatment from the NCDB. **Methods:** Using the NCDB database with patient-level data extraction from 2004 to 2020, we sought to identify the socioeconomic differences, clinical characteristics and examine survival trends for both UC and nUC bladder cancer. **Results:** Majority of UC patients (pts) were M (555107, 75.6%) and 178733 were F; nUC pts had 14296 M and 8835 F, median age was 72 years. 669,669 (or 91.3%) of UC pts were White (W), 5.4% (39444) were Black (B) and nUC pts had 19771 (85.5%) W and 2492 (10.8%) B. 41.2% of UC pts were treated at a Comprehensive Community Cancer Program (CCCP) followed by 28.3% at an academic/research program (ARP) with 20.7% at an integrated network cancer program (INCP) compared to nUC pts at 37.5%, 34.3% and 19.2%, respectively. Most UC pts (65.6%) had Medicare followed by 26.9% with private insurance and 3.2% with Medicaid. Distribution of stage at diagnosis for UC pts were: Stage 0 at 36.9%, Stage I at 16.3%, Stage II & III at 11.8% and Stage IV at 3.6%. While most (51.74%) of F UC pts had stage I, only 12.81% of F nUC had stage I. Majority had Charlson-Deyo Score (CDS) of 0 at 512237 (69.8%). Median Overall survival (mOS) in UC for M was 89.26 months (mos) (CI 88.8-89.76) and for F it was 94.88 mos (CI 93.83-95.93), Log-rank p=0.0011; worse for B = 73.03 mos (CI 71.03 – 74.84) vs W = 90.38 mos (CI 89.95-90.81), Log-rank p<0.0001; mOS was highest for ARP at 96.46 mos (CI 95.54-97.45); CDS of 0 at 108.29 mos (CI 107.66-108.85); private insurance at 185.79 mos (CI 183.98-188.16); mOS for nUC was better for M at 15.64 (CI, 15.05 -16.28) vs F at 12.68 (CI, 12.02, 13.31), Log-rank p<0.001. mOS for metastatic involvement for bone: UC: 5.03 (CI, 4.8, 5.39) vs nUC: 5.42 (4.4, 6.34), Log-rank p=0.2007; brain: U: 3.61 (CI 2.99, 4.3) vs nUC: 5.06 (2.5, 7.13); Log-rank p=0.5765; lung: U: 5.09 (CI, 4.76, 5.39) vs nUC: 4.8 (3.68, 5.78); Log-rank p=0.2163; liver: U: 3.32 (CI,3.06, 3.61) vs nUC: 5.42 (CI, 4.11, 6.44); Log-rank p=0.0009; LN: U: 7.1 (CI, 6.6, 7.56) vs nUC: 6.34 (5.36, 6.9); Logrank p=0.0007; Treatment using surgery, radiation, chemotherapy and immunotherapy all showed improvement in U vs nUC (all Log-rank p<0.0001). **Conclusions:** Women had better survival than men in UC but not in nUC. Factors including lower stages, Whites, private insurance, better CDS scores, treatment at academic/research facility, and lymph node metastases all showed improved survival. These data highlight the importance of bridging the gap between socioeconomic differences to improve outcomes for UC and nUC pts. Research Sponsor: None.

Updated results from a phase II study of penpulimab plus anlotinib as first-line therapy in metastatic urothelial cancer (mUC).

Bo Yang, Qi Xiong, Qi Song, Yaping Long, Gang Guo, Hongzhao Li; Department of Oncology, Chinese PLA General Hospital, Beijing, China; Department of Medical Oncology, Chinese PLA General Hospital, Beijing, China; Medical Ethics Committee of Chinese PLA General Hospital, Beijing, China; Department of Urology, the First Medical Center of Chinese PLA General Hospital, Beijing, China

Background: Cisplatin-based chemotherapy is the standard-of-care systemic treatment for mUC patients with good physical status and organ function, which has shown a response in more than 40% of patients, with mOS approximately 15 months. With the advent of immune checkpoint inhibitors, there are more explorations and options for first-line treatment of locally advanced or mUC. However, here is an ongoing unmet need for improved first-line treatment. Immune checkpoint inhibitors combined with anti-angiogenic therapy have a synergistic effect. Studies have reported that penpulimab combined with anlotinib have good efficacy and safety in multiple solid tumors. This study aimed to evaluate the efficacy and safety of penpulimab plus anlotinib as first-line therapy for mUC (ChiCTR2200056732). **Methods:** In the single-arm, phase II study, eligible patients were aged 18-75 years with mUC who had no prior systemic therapy and ineligible or rejected for cisplatin-based therapy or any platinum-based chemotherapy, measurable lesion (according to RECIST v1.1), and ECOG PS of 0-2. Patients received penpulimab 200 mg intravenously on day 1 and anlotinib 8 mg orally once daily on day 1 to 14 every 3 weeks until progression, intolerable toxicities, or completion of 24 months of treatment. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS) and safety. **Results:** From Feb. 2020 to Dec. 2023, 29 patients of mUC were successfully enrolled and received at least once time treatment. Among them, 79.3% (23/29) were males and 20.7% (6/29) were females, with a median age of 64 years (range, 49-74). 10 of 29 (34.48%) patients had a history of smoking. 24.1% (7/29), 72.4% (21/29) and 3.45% (1/29) patients were ECOG PS 0, 1 and 2, respectively. PD-L1 expression was detected in 25 patients, of whom 52.0% (13/25) had TPS <1, 36.0% (9/25) had TPS$\geq$1%, $<$50%, and 12.0% (3/25) had TPS$\geq$50%. At data cutoff (January. 1. 2024), a total of 24 patients were evaluated with a median follow-up time of 8.3m (95% CI, 2.8-13.8). The ORR was 62.5% (95% CI, 40.6-81.2) and DCR was 95.8% (95% CI, 78.9-99.9). The median PFS was 12.1 months (95% CI, 3.5-20.7). The median OS was not reached and 12-month OS rate was 100%. Frequent treatment-related adverse events of all grades included creatinine increased (16.7%) and transaminase elevation (10.0%). Grade 4 toxicity of liver dysfunction occurred in two patient (6.9%). No treatment-related death was observed. **Conclusions:** Penpulimab plus anlotinib demonstrated promising antitumor activity and manageable safety profile with no new safety signal in mUC. Clinical trial information: ChiCTR2200056732. Research Sponsor: None.

A pilot study of tazemetostat and pembrolizumab in advanced urothelial carcinoma (ETCTN 10183).

Maha H. A. Hussain, Masha Kocherginsky, Parminder Singh, Winston Tan, Zin Myint, Di (Maria) Jiang, Elizabeth Marie Wulff-Burchfield, Yangruijue Ma, Elad Sharon, Richard Piekarz, Joshua J Meeks, David James VanderWeele; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; Division of Biostatistics, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; Mayo Clinic, Phoenix, AZ; Mayo Clinic Florida, Jacksonville, FL; University of Kentucky, Lexington, KY; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; University of Kansas Medical Center, Kansas City, KS; Dana-Farber Cancer, Bethesda, MD; Cancer Therapy Evaluation Program - National Cancer Institute, Bethesda, MD

Background: Mutations of COMPASS-related proteins KMT2D, KMT2C, and KDM6A are observed in 66% of advanced urothelial carcinomas (UC). *In vivo*, the administration of tazemetostat, an enzymatic EZH2 inhibitor (EZH2i), reduced tumor burden and enhanced the immune response in animal models of UC. We hypothesized that tazemetostat might improve response to immunotherapy in advanced UC. **Methods:** ETCTN 10183 (NCT03854474) is a multicenter pilot study evaluating the safety and efficacy of tazemetostat 800 mg BID+ pembrolizumab 200 mg given every three weeks for up to two years in patients (pts) with platinum-refractory (Arm A) or cisplatin/chemo-ineligible advanced UC (Arm B). The primary objective was to identify the recommended phase two dose (RP2D) of tazemetostat in combination with pembrolizumab. Secondary objectives included safety, response rate, and progression-free survival. Translational objectives included determining tumor mutational burden in COMPASS-related genes, tumor subtyping, TCR clonality, T cell infiltration, and PDL-1 expression. **Results:** There were no dose-limiting toxicities in the safety lead-in phase (n=6 pts), and the RP2D for tazemetostat was established at 800 mg BID. Baseline characteristics for Arm A N=12, Arm B N=13: 72% males; 96% white, 4% Black; 88% ECOG PS 0-1; 88% had bladder primary, 20% Stage III, 72% stage IV; 80% had visceral or bone metastases. The median number of cycles was 5 in Arm A (range 1-35) and 4 in Arm B (range 2-12). Treatment related G3/4 adverse events (AEs) were observed in 8 patients, most common were anemia and lymphopenia (n=2 each). Treatment related G1/2 AEs included nausea (n=6); skin and subcutaneous tissue disorders (n=3); anemia, lymphopenia, and thrombocytopenia (n=2 each). Among evaluable patients (n=10 in each arm), partial response rate was: Arm A 30%, Arm B 20%; stable disease: Arm A 30%, Arm B 30%; and progressive disease: Arm A 30%, Arm B 20%. 8 pts were on study treatment for $\geq$ 9 cycles (5 in Arm A, 3 in Arm B). All pts are off protocol treatment. Median progression-free survival was 3.06 (95% CI: 1.38-7.75) months for Arm A and 3.02 (95%CI: 2.4-5.65) for Arm B. **Conclusions:** Tazemetostat 800 mg BID and pembrolizumab combination is feasible and well-tolerated in patients with advanced UC. In this pilot study, improvement in efficacy relative to historical controls of pembrolizumab alone appears to be modest. Response in tumors with COMPASS-related mutations and EZH2 activity will be evaluated. Clinical trial information: NCT03854474. Research Sponsor: National Cancer Institute.

Evorpacept plus enfortumab vedotin in patients (Pts) with locally advanced or metastatic urothelial carcinoma (la/mUC): Phase 1a dose escalation results.

Samuel A Funt, Petros Grivas, Xin Gao, Daniel A. Vaena, Tian Zhang, Matthew I. Milowsky, Mayank Rao, Harry Liu, Kimberly Tipton, Grace An, Feng Jin, Alison J Forgie, Sophia Randolph, Athanasios C. Tsiatis, Rohit K. Jain; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Division of Hematology/Oncology, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA; West Cancer Center and Research Institute, Memphis, TN; Division of Hematology and Oncology, Department of Internal Medicine, University of Texas Southwestern, Dallas, TX; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; ALX Oncology Inc., South San Francisco, CA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Maximizing antibody dependent cellular phagocytosis (ADCP) in the tumor microenvironment requires both the inhibition of the myeloid CD47/SIRPα checkpoint and activation of the macrophage's FcyR by an anti-cancer specific antibody (Lakhani et al. *Lancet Oncol* 2021). Evorpacept (EVO) is a CD47 inhibitor with an inactivated Fc effector domain that blocks the CD47-SIRPα interaction. Enfortumab vedotin (EV) is a nectin-4-directed antibody drug conjugate (ADC) which engages the FcyR on the macrophage. We evaluated whether EVO plus EV would be safe, tolerable and active in pts with la/mUC. **Methods:** 20 pts with la/mUC who had received prior platinum-based chemotherapy and progressed during or after treatment with a PD-1/L1 inhibitor were administered study drug in this phase 1 study (NCT05524545). Dose escalation (DE) cohorts were administered intravenous (IV) EVO 20 mg/kg or 30 mg/kg Q2W plus standard EV 1.25 mg/kg IV on days 1, 8 and 15 of a 28-day cycle. The primary endpoint was first cycle dose limiting toxicity (DLT) using a Bayesian Optimal Interval design. Additional pts were enrolled in both dose levels as backfill cohorts to further characterize safety, PK, PD, and preliminary antitumor activity. Investigator response was based on RECIST v1.1, and data cut off was 18Jan(safety)/24Jan(efficacy) 2024. **Results:** Fourteen pts were administered EVO 20 mg/kg Q2W (DE n= 3; backfill n=11) and 6 pts EVO 30 mg/kg Q2W (DE n=6) plus standard EV. No DLTs were observed, and the maximum tolerated dose (MTD) of the combination was not reached. The maximum administered dose (MAD) of EVO was 30 mg/kg Q2W combined with EV. There were no treatment-related deaths on study. Treatment emergent adverse events (TEAEs) occurring in $>$ 25% of subjects included fatigue, diarrhea, abnormal loss of weight, dysgeusia, decrease appetite, hyperglycemia, constipation, hypomagnesemia, lacrimation increased, nausea, peripheral sensory neuropathy, rash maculo-papular and urinary tract infection (UTI). There were 3 serious adverse events that were related to EVO plus EV (G3 UTI [1 pt]; G4 neutrophil count decreased and G3 UTI [1 pt]). Sixteen patients were response evaluable. The overall response rate (ORR) was 63% (1CR, 9PR). Accrual is ongoing and updated data will be provided at the time of presentation. **Conclusions:** This is the first study, to our knowledge, reporting data on the combination of a CD47 blocking agent in combination with an ADC in la/mUC. EVO plus EV is well tolerated at doses evaluated with no MTD reached and a MAD of 30 mg/kg Q2W. The combination shows early promising clinical activity compared to an ORR of 41% with EV alone in pts with la/mUC who had previously received platinum-based chemotherapy and a PD-1/L1 inhibitor (Powles et al. *N Engl J Med* 2021). Further investigation in this refractory population, including patients with prior EV exposure, is warranted. Clinical trial information: NCT05524545. Research Sponsor: ALX Oncology Inc.

SOGUG-Vexillum: Phase II non-randomized clinical trial of nivolumab/ipilimumab maintenance following first-line chemotherapy in unresectable locally advanced or metastatic urothelial cancer.

Guillermo de Velasco, Iciar García Carbonero, Urbano Anido, Juan Antonio Virizuela, Carlos Álvarez-Fernández, Francisco José Álvarez-Márquez, Marina Justo de la Peña, Rebeca Lozano, Pablo Gajate, Oscar Reig, Aina Iranzo, Eduardo Pujol; Medical Oncology Department, Hospital Universitario 12 De Octubre, Madrid, Spain; Medical Oncology Department, Hospital General Universitario de Toledo, Toledo, Spain; Medical Oncology, University Clinical Hospital of Santiago de Compostela, Santiago De Compostela, Spain; Medical Oncology Department, Hospital Universitario Virgen de la Macarena, Sevilla, Spain; Medical Oncology Department, Hospital Universitario Central de Asturias, Oviedo, Spain; Medical Oncology Department, Hospital Universitario Juan Ramón Jiménez, Huelva, Spain; Medical Oncology Department, Hospital Universitario Son Espases, Mallorca, Spain; Medical Oncology Department, Complejo Asistencial Universitario de Salamanca; Institute for Biomedical Research of Salamanca (IBSAL), Salamanca, Spain; Medical Oncology Department, University Hospital Ramón y Cajal, Madrid, Spain; Medical Oncology Department, Hospital Clinic de Barcelona; Translational Genomics and Targeted Therapeutics in Solid Tumors Lab, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); Department of Medicine, University of Barcelona, Barcelona, Spain; Medical Oncology Department, Hospital Universitario de la Ribera, Alzira (Valencia), Spain; Medical Oncology Department, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

Background: Nivolumab (nivo) 1mg/kg plus ipilimumab (ipi) 3mg/kg achieved the highest ORR (42.4%) in refractory metastatic urothelial carcinoma (mUC) with a manageable safety profile. The addition of nivo and ipi subsequently to first-line chemotherapy (CT) could consolidate the clinical benefit. **Methods:** This single arm, open-label, multicenter study evaluates the effectiveness of ipi 3 mg/kg and nivo 1 mg/kg (Q3W) for 4 cycles followed by nivo maintenance therapy (Q4W) in delaying disease progression in patients with unresectable urothelial cancer that did not progress after first-line platinum-based CT (at least 4-6 cycles of CT). Autoimmune disease, immune deficiency, and symptomatic brain metastasis were excluded. The primary endpoint is Progression Free Survival (PFS) in intention-to-treat and PD-L1 populations. Secondary endpoints include: objective response rate (ORR), duration of response (DoR), overall survival (OS), overall survival from 1st dose of CT (cOS), progression-free survival from 1st dose of CT (cPFS), safety and translational biomarker analysis. Sample size was estimated using a Simon II stage design for 4-months PFS rate (H0= 40%; H1= 60; α= 0.05; β= 80%; attrition 10%), requiring 25 patients in the 1st stage and up to 66 in total. Here we report the interim analysis for 1st stage. **Results:** As of January 2024, the 1st accrual stage was completed with 25 evaluable patients. Baseline characteristics are outlined in the table. With a median follow-up of 6.8 months (95% CI: 6.2-10.5), the 4-m PFS rate was 64% (95% CI: 47.7-85.9) and the median PFS was 4.3 months (95% CI: 3.2-NR). The median cPFS was 9.4 months (95% CI: 8-NR). The 6-m OS rate was 76.4% (95% CI: 60-97.2), while median cOS was 15.4 months (95% CI: 15.4-NR). The median duration of treatment was 2.6 months (95% CI: 2.1, 5.7). Nivo and ipi were permanently discontinued due to toxicity in 3 (12%) and 1 (4.2%) patients, respectively. Nivo doses were delayed in 8 (32%) patients and ipi in 3 (12%) for management of toxicity. Grade $\geq$3 toxicities were reported in 8 (32%) patients, being the most common: Immune-mediated hepatitis (8%), ALT/AST increased (8%) and diarrhea (8%). **Conclusions:** Maintenance treatment with nivo and ipi showed preliminary efficacy consolidating clinical benefit to CT with a manageable safety profile. The 4-m PFS rate surpassed the futility threshold in the interim analysis and the accrual in Stage II is underway. Final survival results are awaited. Clinical trial information: NCT05219435. Research Sponsor: SOGUG through industry collaborator BMS.

Median age (range); years	64 (53-79)
Male; n (%)	20 (80)
ECOG; n (%)	
0	13 (52)
1	12 (48)
CT; n (%)	
Gemcitabine-Carboplatin	11 (44)
Gemcitabine-Cisplatin	14 (56)
Best response to CT; n (%)	
CR	4 (16)
PR	12 (48)
SD	9 (36)

Association of ephrinB2 (B2) expression on overall survival (OS) and resistance to PD1/L1 inhibitors (inh) in metastatic urothelial carcinoma (mUC).

Sarmad Sadeghi, Nataliya Mar, Denice Tsao-Wei, Karam Ashouri, Imran Siddiqi, Jon P Cogan, Alexandra Jackovich, Dory Freeman, Jillian O'Toole, Thomas W. Flaig, parkash S. gill, Arash Rezazadeh, Guru P. Sonpavde, Joaquim Bellmunt; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; University of California, Irvine Medical Center, Orange, CA; University of Southern California, Los Angeles, CA; Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Vasgene Therapeutics, Inc, Los Angeles, CA; Rutgers New Jersey Medical School, Newark, NJ; Dana-Farber Cancer Institute, Boston, MA; University of Colorado Anschutz Medical Campus, Aurora, CO; AdventHealth Cancer Institute, Orlando, FL

Background: B2 is a ligand for EphB4 (B4) which enhances tumor invasion, proliferation, survival and promotes angiogenesis. TCGA data (N= 409) bladder cancer patients (pts) showed B2 high expression (34%) had poor OS vs. low expression (66%) (Hazard Ratio- HR- 0.7 p=0.02). Our phase II trial of sEphB4-HSA, a B2 inhibitor, combined with pembrolizumab in pre-treated mUC (N=70) showed an objective response rate (ORR) of 37%. Pts with high B2 had 52% ORR with 24% complete response (CR) (JCO PMID 35984996). This retrospective study examined the OS and ORR to PD1/L1 inh in pts with mUC and its correlation with B2 expression. **Methods:** Pts with mUC who received PD1/L1 inh were eligible if they had radiographic response data and tumor tissue for B2 testing. Demographics and disease characteristics were abstracted. Radiographic was assessed using RECIST 1.1. Tumor specimens were analyzed for B2 expression using in-situ hybridization (ISH). Scores of 2-4 were marked High (Hi) and 0-1 Low (Lo). Descriptive statistics summarized the results. Cox Model, logrank and Fisher's exact test were used for the association of B2 status with OS and ORR, respectively, using SAS 9.4. **Results:** 143 (N) pts from University of Southern California (USC, n = 49), Dana Farber (DFCI, n = 55), and University of California, Irvine (UCI, n = 39) were included. 101 pts were male (71%). Median age was 73. PD1/L1 inh included pembrolizumab (n = 111, 78%), atezolizumab (n = 25, 17%), nivolumab, avelumab, and durvalumab in 3%, 1%, and 1%, respectively. ORR defined as CR + partial response (PR) was 21% (95% CI 14%, 29%) (N = 136 evaluable). ORR was 12% vs 33% in B2 Hi vs Lo, p = 0.005. The median OS was 17.2 months (mo) (95% CI 13.5, 23.8) (N = 143). Median OS was 14.5 (95% CI 9.4, 21.0) mo vs 24.0 (95% CI 13.7, 60.8) mo for B2 Hi vs Lo, logrank p = 0.022 (HR 1.65 95% CI:1.07, 2.55 Wald p = 0.023). **Conclusions:** B2 Hi is associated with poor OS and poor ORR in PD1/L1 inh monotherapy treated mUC acting as a biomarker of disease outcome. These data suggest B2-B4 pathway to be a mechanism of resistance to PD1/L1 inh and a therapeutic target. Research Sponsor: None.

	Subgroups				P
B2 Any	All, N=143 100%	USC, n=49 100%	DFCI, n=55 100%	UCI, n=39 100%	
Median Age (range)	73 (48-91)	72 (48-87)	73 (48-91)	74 (48-90)	0.82
Male (%)	101 (71%)	37 (76%)	36 (65%)	28 (72%)	0.53
ECOG 0, 1, >1 (%)	42, 35, 23	51, 22, 27	40, 40, 21	33, 44, 23	0.23
Visceral Metastases (%)	79 (55%)	26 (53%)	36 (65%)	17 (44%)	0.11
ORR*	28 (21%)	10 (20%)	11 (20%)	7 (22%)	1.00
B2 Lo	55 (40%)	21 (43%)	19 (35%)	15 (47%)	0.005
ORR	18 (33%)	6 (29%)	7 (37%)	5 (33%)	
B2 Hi	81 (60%)	28 (57%)	36 (65%)	17 (53%)	
ORR	10 (12%)	4 (14%)	4 (11%)	2 (12%)	
OS (mo.) Median (95% CI)	17.2 (13.5, 23.8)	16.0 (8.1, 30.1)	14.5 (9.0, 18.0)	32.0 (13.3, 60.8)	0.32
B2 Lo	60 (42%)	21 (43%)	19 (35%)	20 (51%)	0.022
OS	24.0 (13.7, 60.8)	24.0 (9.2, NA)	17.5 (7.3, 27.6)	45.1 (10.8, 60.8)	
B2 Hi	83 (58%)	28 (57%)	36 (65%)	19 (49%)	
OS	14.5 (9.4, 21.0)	8.8 (3.8, 30.1)	13.8 (8.2, 16.7)	21.0 (9.4, 32.8)	

*7 pts inevaluable

FGFR3 alterations (FGFRalt) in patients (pts) who develop locally advanced or metastatic urothelial cancer (mUC), and their association with tumor subtype and clinical outcomes in pts treated with erdafitinib (erda) vs. pembrolizumab (pembro).

Arlene O. Siefker-Radtke, Yohann Loriot, Nobuaki Matsubara, Se Hoon Park, Robert A Huddart, Earle F Burgess, Jiarui Zhang, Neil Beeharry, Shibu Thomas, Nicole L. Stone, Kris Deprince, Spyros Triantos, Woonyoung Choi; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Université Paris-Sud, Université Paris-Saclay, Gustave Roussy, Villejuif, France; National Cancer Center Hospital East, Chiba, Japan; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Section of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Medical Oncology Department, Levine Cancer Institute, Charlotte, NC; Janssen Research & Development, Spring House, PA; J&J Innovative Medicine, Spring House, PA; Johnson and Johnson Innovative Medicine, Spring House, PA; J&J Innovative Medicine, Beerse, Belgium; Greenberg Bladder Cancer Institute, Johns Hopkins Medical Institutions, Baltimore, MD

Background: Erda, an oral pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor is approved to treat adult pts with locally advanced or mUC with susceptible *FGFR3alt*, whose disease progressed on or after at least one line of prior systemic therapy. In superficial and surgically resectable UC, *FGFRalt* has been shown to be highly associated with luminal subtype characterized by expression of luminal markers, low expression of basal markers and with immune cold / poor immune infiltration. In a randomized open-label phase III THOR study (Cohort 2), erda showed improvement in objective response and progression-free survival (PFS) compared to pembro, with no significant improvement in overall survival (OS). Exploration of subtypes in a large cohort of mUC pts has not been done and so a molecular analysis was undertaken to further understand the clinical findings. **Methods:** All available tumors from pts enrolled in Cohort 2 (*FGFRalt* positive; N = 201) and a subset of FGFR wildtype (N = 116) were used to perform whole transcriptome RNA sequencing, where 152 and 84, respectively, passed quality control. The consensus single-sample classifier was applied to the RNAseq data to determine molecular subtypes. Tumor subtypes was correlated with treatment response to erda or pembro, PFS and OS. **Results:** Molecular classification of tumors identified a significant proportion of luminal-papillary (LumP) subtype in the tumors harboring *FGFRalt* compared to FGFR WT (78.3% vs. 36.9%, $p < 0.001$) vs. other subtypes: basal/squamous (Ba/Sq; 11.2% vs. 31.0%), stroma-rich (6.6% vs. 10.7%), neuroendocrine-like (0% vs. 2.4%), luminal-unstable (3.3% vs. 17.9%) and luminal-unspecified (0.7% vs. 1.2%), respectively. Consistently, *FGFRalt* type showed differential association with subtypes: 3.2% of fusions and 14.1% of mutations were detected in Ba/Sq subtype while 74.2% and 79.3%, respectively, were detected in LumP. Clinical outcomes evaluated within LumP subset showed a significant improvement in ORR of erda-treated vs. pembro-treated pts (41.7 vs. 19.7%; $p = 0.01$), which was consistent with the intent to treat (ITT) population (40.0% vs. 21.6%). Numerical improvement were observed in PFS in the LumP subtype between erda vs. pembro (5.5 vs 2.7 months) compared with the ITT population (4.4 vs 2.7). However, the benefit of erda over pembro in the LumP subtype did not translate to OS (10.9 vs. 12.9 months), similar to the ITT population (10.9 vs. 11.1 months). **Conclusions:** A significant overlap was identified between genomic selection of *FGFRalt* and the LumP subtype. Clinical outcomes based on transcriptomic analyses were consistent with those observed in the ITT population. These findings warrant further understanding of LumP tumors and association to treatment response. Clinical trial information: NCT03390504. Research Sponsor: Janssen Research & Development.

Inferring PDL-1 status from H&E images using digital pathology to identify patients responsive to anti-PD(L)-1 immuno-oncology therapy for bladder cancer trials.

Albert Juan Ramon, Brandon Ginley, Madhawa Saranadasa, Chaitanya Parmar, Neil Beeharry, Shibu Thomas, Bolan Linghu, Joel Greshock, Kristopher Standish; J&J Innovative Medicine, San Diego, CA; J&J Innovative Medicine, Raritan, NJ; J&J Innovative Medicine, Spring House, PA; Janssen Research & Development, Spring House, PA; Johnson & Johnson Innovative Medicine, Cambridge, MA; Research & Development, Johnson and Johnson Innovative Medicine, Raritan, NJ; Johnson and Johnson Innovative Medicine, San Diego, CA

Background: Programmed death ligand-1 (PDL-1) expression has been established as a biomarker for response to immune checkpoint inhibitors in bladder cancer. Targeted therapies that inhibit the PDL-1 pathway improve therapeutic response, but immunohistochemistry (IHC) testing is required to assess PDL-1 expression. In order to ease identification of patients who have high potential to respond to anti-PD(L)-1 therapies, we explore the use of a computer vision algorithm to infer PDL-1 expression from patients routine H&E images. **Methods:** We pretrained a Foundational Model on ~55k unlabeled WSIs from various sources (multiple scanners, hospitals, diseases, tissues..). We then finetuned it on a train set (n=1546) of PDL-1 labeled H&E images to infer expression. Labels were defined as PDL1-High or PDL1-Low based on the most sensible threshold for the various included antibodies (e.g., TPS>=10% on 22C3 antibody, CPS>=1% on 28-8 antibody, etc..). We applied this model to WSIs from 1) a holdout split (n=388) and 2) an independent dataset (n=93) to evaluate the performance at inferring PDL1-High vs. PDL1-Low, quantified by the Area Under ROC Curve (AUC). We then applied the model to a third dataset (n=27) containing WSIs from bladder cancer patients taken prior to start of anti-PD(L)-1 treatment (i.e., pembrolizumab) and evaluated treatment response (quantified by overall survival) for the two stratified groups based on the model outputs (PDL1-High vs. PDL1-Low). Results were compared to patients stratified based on IHC pathology readouts (i.e., TPS>=10% vs. TPS<10%). **Results:** For PD-L1 status inference, the model achieved AUC=0.82 and AUC=0.8 on holdout and independent datasets respectively. The table below shows survival analysis results upon pembrolizumab treatment (n=27) when stratifying patients based on the algorithm (AI-based PDL1-High vs. PDL1-Low) compared to IHC-based stratification. Note that the survival probability for PDL1-High patients is higher than PDL1-Low patients. **Conclusions:** We developed a computer vision algorithm to infer PDL-1 expression from routine H&E images. The algorithm shows strong performance at classifying PDL-1 status and proficiency in inferring outcomes to anti-PD(L)-1 therapy in a small bladder cancer data set. This tool represents a novel, rapid means to assess whether a patient may respond to anti-PD(L)-1 therapies from common H&E-stained images and has the potential to guide patient care decisions in clinic. Research Sponsor: None.

	Survival Probability [95% CI]			
Method	**6 Month**	**12 Month**	**24 Month**	**p-value**
AI-based PDL1-High	**0.89** [71, 100] (n=7)	**0.76**[52, 100] (n=5)	**0.76** [52, 100] (n=4)	**0.12**
AI-based PDL1-Low	**0.55** [35, 87] (n=8)	**0.40** [21, 76] (n=5)	**0.40** [21, 76] (n=4)	
IHC-based (TPS>=10%)	**0.49** [23, 100] (n=3)	**0.32** [11, 97] (n=2)	**0.32** [11, 97] (n=2)	**0.25**
IHC-based (TPS<10%)	**0.76** [58, 100] (n=12)	**0.62** [42, 92] (n=8)	**0.62** [42, 92] (n=6)	

Response and outcomes with immune checkpoint inhibitor (ICI) in patients (pts) with urothelial carcinoma (UC) and subtype histology (SH).

Dimitra Rafailia Bakaloudi, Dimitrios Makrakis, Rafee Talukder, Leonidas Nikolaos Diamantopoulos, Tanya Jindal, Charles B Nguyen, Charbel Hobeika, Vinay Mathew Thomas, Jeffrey Johnson, David Humberto Marmolejo Castañeda, James Korolewicz, Roubini Zakopoulou, Gavin Hui, Pedro C. Barata, Lucia Andrea Alonso Buznego, Jason R Brown, Tyler F. Stewart, Ilana B. Epstein, Ali Raza Khaki, Petros Grivas; Division of Oncology, Department of Medicine, University of Washington, Seattle, WA; Department of Medicine, NYC Health + Hospitals/Jacobi, Albert Einstein College of Medicine, Bronx, NY; Baylor College of Medicine, Houston, TX; Mayo Clinic Rochester, Rochester, MN; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; Rogel Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Division of Oncology, Department of Medicine, University of Iowa, Iowa City, IA; Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Imperial College London, Department of Surgery & Cancer, London, United Kingdom; Attiko Hospital, Athens, Greece; University of California, Los Angeles, Los Angeles, CA; University Hospitals Seidman Cancer Center, Cleveland, OH; Marqués de Valdecilla Universitary Hospital, Santander, Spain; Division of Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH; University of California, San Diego Health, La Jolla, CA; Dana-Farber Cancer Institute, Boston, MA; Stanford University, Stanford, CA; Department of Medicine, Division of Hematology/Oncology, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: ICIs are used for UC in different settings. Most cases have pure urothelial carcinoma (PUC) but about a third have UC mixed with SH. We examined pts with UC treated with ICI and hypothesized that outcomes would not differ between PUC and mixed with SH. **Methods:** We retrospectively included pts with PUC and any SH component treated with ICI as adjuvant, 1st line [1L] upfront, maintenance avelumab [mAV], ≥2nd line [2+L] therapy; pts were divided by SH type. Pts with multiple SH were included as separate group. We excluded pts with pure non-UC histology and pts treated with neoadjuvant ICI. We calculated overall response rate (ORR), median overall, progression-free and disease-free survival [mOS, mPFS, mDFS] using KM method from ICI start. Analysis was stratified by therapy line; multivariable models were adjusted by Khaki factors for 1L/upfront, mAV and Bellmunt factors for 2+L; reference group was PUC. We used descriptive statistics for small subsets. **Results:** We included 1525 pts from 26 sites; n=752 1L, n=609 2+L; 76% men, 80% White, 69% smoking history, 80% lower urinary tract primary, 28% SH. Median f/u time from 1L ICI start 24 months (mo): mPFS was 3 (95%CI 2.8-3.2) mo for PUC (n=340), 3 (95%CI 2-4) mo for squamous (n=60) (HR=1, [95%CI 0.7-1.4]), 2 (95%CI 1.4-3.2) mo for micropapillary (n=36) (HR=1.3 [95% 0.9-2]) and 4 (3.5-4.5) mo for ≥2 SH (n=20) (HR=0.9 [95%CI 0.6-1.5]). Median f/u time from 2+L ICI start 26 mo: mPFS was 3 (95%CI 2.4-3.2) mo for PUC (n=264), 4 (95%CI 2-5) mo for squamous (n=33) (HR=0.8, [95%CI 0.6-1.2]), 3 (95%CI 1.6-3.7) mo for micropapillary (n=17) (HR=0.9 [95% 0.6-1.7]) and 3 (2.5-3.1) mo for ≥2 SH (n=10) (HR=1.2 [95%CI 0.6-2.2]); Table shows ORR/OS data. Data on adjuvant and mAV settings will also be presented. **Conclusions:** We found no significant survival difference between PUC and SH. ORR was numerically higher with sarcomatoid SH and ≥2 SH in the 1L upfront setting. Limitations: retrospective design, small sample size in a few subsets, lack of randomization and central scan/path (% SH) review, selection bias, unmeasured confounders. Research Sponsor: None.

	1L Upfront				2+L			
	ORR (%)	OR (95%CI)	mOS (mo)	HR (95%CI)	ORR (%)	OR (95%CI)	mOS (mo)	HR (95%CI)
PUC	31 (157/508)		15 (12-17)		21 (93/442)		9 (8-10)	
Squamous	27 (21/79)	0.9 (0.5-1.6)	15 (8-23)	1.2 (0.8-1.6)	20 (12/60)	1 (0.5-2)	9 (6-12)	1.1 (0.8-1.6)
Micropapillary	20 (9/46)	0.6 (0.3-1.4)	11 (6-17)	1.3 (0.9-1.9)	25 (9/36)	1.2 (0.5-3)	6 (1-11)	1.1 (0.7-1.7)
Plasmacytoid	27 (4/15)	1.2 (0.4-3.6)	15 (12-19)	0.8 (0.4-1.8)	17 (1/6)	1.4 (0.1-13)	11 (5-17)	1.1 (0.4-3.7)
Sarcomatoid	50 (6/12)	1.2 (0.3-5)	13 (0.1-45)	1.2 (0.5-3.0)	22 (2/9)	1.4 (0.3-7)	5 (4-7)	1.3 (0.6-2.7)
Small cell-NE	13 (1/8)	0.4 (0.04-3.2)	10 (2-17)	1.3 (0.6-2.8)	17 (1/6)	0.8 (0.01-7)	3 (1-5)	3.2 (1.3-8)
Glandular	13 (1/8)	0.3 (0.04-2.9)	4 (NA)	1.4 (0.5-3.8)			5 (4-6)	2.3 (0.9-5.7)
≥2 SH	48 (15/31)	2 (0.9-4.6)	21 (12-30)	0.9 (0.5-1.5)	5 (1/19)	0.2 (0.3-1.8)	7 (4-10)	1.6 (0.9-2.9)

Clinical outcomes of sacituzumab govitecan (SG) after prior exposure to enfortumab vedotin (EV) in patients with metastatic urothelial carcinoma (mUC).

Michal Sternschuss, Nicolas Toumbacaris, Jeeban Paul Das, Thomas Powles, Dean F. Bajorin, Ritesh R Kotecha, Andrew Leonard Laccetti, Han Xiao, Emily Feld, Deaglan Joseph McHugh, Niamh M. Keegan, Samuel A Funt, Neil J. Shah, Gopa Iyer, David H Aggen, Min Yuen Teo, Irina Ostrovnaya, Jonathan E. Rosenberg; Memorial Sloan Kettering Cancer Center, New York, NY; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Memorial Sloan Kettering Cancer Center at Basking Ridge New Jersey, Basking Ridge, NJ

Background: SG is a TROP-2 directed antibody-drug conjugate (ADC) approved as advanced-line treatment for mUC after platinum-based chemotherapy and a checkpoint inhibitor, based on phase II study (TROPHY-U-01) that demonstrated objective response rate (ORR) of 28%, median progression free survival (PFS) of 5.4 months (mo) and median overall survival (OS) of 10.9 mo. Current guidelines for mUC endorse using SG in post EV setting, more so with the recent FDA approval of EV and pembrolizumab as the new standard of care for 1st line. Data is scarce regarding the efficacy of SG in patients previously treated with EV, as only 10 patients (8.8%) included in TROPHY-U-01 cohort 1 had prior EV exposure. Here, we report real-world clinical outcomes for SG post EV. **Methods:** This is a single center retrospective cohort of patients with mUC treated with SG after prior exposure to EV. Demographics and clinical data were collected retrospectively by chart review. Clinical response to SG and EV was defined by physician assessment. Cases with objective response to SG per clinical review [complete response (CR) + partial response (PR)] were then confirmed by formal radiological evaluation using RECIST 1.1. PFS and OS defined from start of SG were calculated using the Kaplan-Meier method. **Results:** 82 patients were identified, median age was 71 years (range 47-83), 70% male and 37% upper tract primary. Lung, bone, liver and brain metastases were present in 67%, 62%, 50% and 13% of patients, respectively. Median prior treatment lines were 3 (range 1-8), 68% of patients received SG directly post EV. Most patients were treated with single agent EV, though 8 patients (10%) received combination of EV + pembrolizumab. PR was confirmed in 8 patients, and none had CR, resulting in an ORR of 10% (95% CI 4.3%, 18.3%). Stable disease (SD) was achieved in 16 patients (20%, 95% CI 11.9%, 30.4%) amounting to disease control rate (DCR = CR+PR+SD) of 30% (95% CI 20.3%, 41.3%). Median PFS was 2.1 mo (95% CI 1.9, 2.5) and median OS was 6.0 mo (95% CI 4.5, 7.0). There was no association between response to EV and ORR, PFS or OS after SG ($p>0.8$). Sequencing SG directly after EV was associated with improved ORR ($p = 0.028$) and PFS (HR=0.43, 95% CI 0.21, 0.87, $p=0.02$, adjusted for tumor location, treatment line and liver metastasis) but not OS. Dose reductions were required upfront in 18%, on treatment in 44% or both in 7%. Prophylactic granulocyte stimulating factor (GCSF) was used in 57 patients (70%), rates of G3-4 neutropenia, anemia and thrombocytopenia were 36%, 36% and 4% respectively. **Conclusions:** In our large cohort of real-world advanced mUC patients with prior exposure to EV, SG resulted in limited clinical efficacy compared to previous reports. There was an association between SG administration directly after EV and improved clinical outcomes. Further investigations are warranted to explore optimal treatment sequencing. Research Sponsor: None.

Multi-omic analysis of the prognostic and predictive value of *LAG3* expression in urothelial carcinoma.

Adanma Ayanambakkam, Anh B. Lam, Kieran Sweeney, Chao Xu, Andrew Elliott, Seven Tomek, Chadi Nabhan, Sumati Gupta, Jad Chahoud, Debasish Sundi, William Paul Skelton IV, Laura Graham, Lyudmyla Derby Berim, Bodour Salhia, Sean Kern, Stephen B. Edge, Yousef Zakharia, Abhishek Tripathi, Rana R. McKay, Abdul Rafeh Naqash; Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Caris Life Sciences, Irving, TX; Caris Life Sciences, Phoenix, AZ; Caris Life Sciences and the University of South Carolina, Deerfield, IL; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Department of Genitourinary Medical Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The Ohio State University, Columbus, OH; University of Virginia Comprehensive Cancer Center, Charlottesville, VA; University of Colorado Cancer Center Anschutz Medical Campus, Aurora, CO; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Department of Translational Genomics, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Indiana University, Indianapolis, IN; Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY; University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA; Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; University of California, San Diego Health, La Jolla, CA; University of Oklahoma Health Sciences Center, Stephenson Cancer Center, Oklahoma City, OK

Background: Lymphocyte-activation gene 3(*LAG3*) is an immune checkpoint protein expressed on immune cells that inhibits T-cell function. Despite its established prognostic significance in other malignancies, the role of *LAG3* as a prognostic or predictive biomarker in urothelial carcinoma (UC) remains inadequately studied. **Methods:** DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing were performed for patient tumors submitted to Caris Life Sciences. PD-L1+ status (22c3, combined positive score≥10) was determined by IHC. TMB-High (TMB-H) was defined as ≥10 mutations/Mb. *LAG3* high (*LAG3*-H) and low (*LAG3*-L) groups were defined by the top and bottom quartiles of *LAG3* RNA transcripts per million, respectively. Tumor microenvironment (TME) cell fractions were estimated by RNA deconvolution using quanTIseq. Significance was tested using Mann-Whitney U and $?^2$ tests as appropriate. Real-world median overall survival (mOS) was obtained from insurance claims data and calculated from treatment start to last contact, while time-on-treatment (ToT) was calculated from treatment start to end. Hazard ratio (HR) was calculated using the Cox proportional hazards model, and p-values were calculated using the log-rank test. Clinical and RNA-seq data from patients enrolled in the Oncology Research Information Exchange Network (ORIEN) were used to validate the analysis. **Results:** Among 3343 UC cases, *LAG3*-H was associated with increased *TP53* (70.6% vs 49.4%, $q<10^{-4}$) and *RB1* mutations (31.0% vs 18.0%, $q<10^{-4}$), decreased *FGFR3* mutations (6.0% vs 18.1%, $q<10^{-4}$), and increased TMB-H (50.1% vs 36.7%, $q<10^{-4}$) and PD-L1+ status (71.0% vs 16.2% 22c3, $q<10^{-4}$). *LAG3*-H tumors had increased infiltration of CD8+ (1.5% vs 0.0%, $q<10^{-4}$) and NK (2.3% vs 1.6%, $q<10^{-4}$) cells, but also higher levels of inhibitory Tregs (3.3% vs 1.4%, $q<10^{-4}$). No significant difference was found in mOS of patients with LAG3-H, when comparing low vs high levels of FGL1 expression (HR=0.934, p=0.51). Among patients who received an immune checkpoint inhibitor (ICI; N=675), multivariate analysis using Cox proportional hazard regression revealed that *LAG3*-H had improved mOS vs *LAG3*-L (HR=0.720, p=0.002) after accounting for potential confounders (sex, TMB, *TP53*, and *FGFR3*). *LAG3*-H also had significantly improved mOS vs *LAG3*-L in PD-L1+ patients given ICI (N=291, HR=0.605, p=0.009). *LAG3* expression was also higher in patients with above median ToT on avelumab (1.4-fold, p=0.049) and pembrolizumab (1.2-fold, p=0.022). Improved mOS for *LAG3*-H vs LAG3-L patients (HR=0.65, p=0.036) were validated using the ORIEN database. **Conclusions:** Increased *LAG3* expression in UC correlates with a distinct mutational landscape, an inflamed TME characterized by augmented immune cell infiltration, prolonged ICI ToT, and significant improvements in mOS. These findings corroborate the potential for dual LAG3 PD1 blockade in UC. Research Sponsor: None.

Disparities in trends in bladder cancer mortality between urban and rural patients: A 2000-2020 analysis.

Abdul Rahman Al Armashi, Marisa Thierheimer, Laura Bukavina, Adam C. Calaway, Randy Vince, Prateek Mendiratta, Jorge A. Garcia, Jason R Brown; Seidman Cancer Center, Case Western Reserve University, Case Comprehensive Cancer Center, Cleveland, OH; Case Western Reserve University School of Medicine, Cleveland, OH; University Hospitals, Cleveland Medical Center, Cleveland, OH; University Hospitals Seidman Cancer Center, Cleveland, OH; University Hospitals and Case Western Reserve University, Cleveland, OH; University Hospitals of Seidman Cancer Center/Case Comprehensive Cancer Center, Cleveland, OH

Background: Patients in rural areas in the US often have worse healthcare outcomes due to socioeconomic deprivation, higher rates of smoking, and limited access to medical care. Despite a general decline in bladder cancer mortality over the past two decades, comprehensive studies comparing these trends between urban and rural mortality are scarce. **Methods:** Utilizing the CDC WONDER database, we extracted mortality data for bladder cancer from 2000 to 2020. Age-adjusted mortality rates per 100,000 persons were standardized to the Year 2000 US standard population. Data segmentation by urbanity utilized the 2013 National Center for Health Statistics Urban-Rural Classification Scheme. The National Cancer Institute's Joinpoint Regression Program was employed to calculate average annual percent changes (AAPCs) and annual percent changes (APCs). **Results:** In our analysis, we identified a total of 306,750 bladder cancer death cases from 2000 to 2020. Significant improvements in bladder cancer mortality were observed in urban areas, with large central metros experiencing the most pronounced decrease (AAPC -1.0%, $p<0.001$). This decline was moderate between 2000 and 2016 (APC -0.3, $p< 0.001$) but accelerated between 2016 and 2020 (APC -3.8%, $p<0.001$). Large fringe and medium metros also saw comparatively smaller but significant declines (AAPC -0.6%, $P<0.05$) and also accelerated between 2016-2020. In contrast, small metro and rural areas (micropolitan and noncore) showed no significant improvement, with mortality rates remaining stable between 2000 and 2020 (AAPC 0.2%, P=0.099). **Conclusions:** This analysis, the largest to date comparing urban and rural mortality trends in bladder cancer, highlights significant disparities in outcomes between large urban and rural areas. The marked improvement in urban areas, especially noted around the time novel agents such as immunotherapy were introduced, underscores the potential impact of advanced treatments. However, the stable mortality rates in rural areas suggest that access to advanced care, environmental influences, socioeconomic status, and slower adaptation of new guidelines in rural settings may play critical roles. These findings underline the urgent need for strategies to close the urban-rural gap. Research Sponsor: None.

Bladder cancer mortality trends by location (2000-2020).

Location	AAPC (%)	Joinpoints APC% (Years Specified)	P-Value
Large Central Metro	-1.0	-3.8 (2016-2020)	<0.001
Large Fringe Metro	-0.6	-2.6 (2016-2020)	0.016
Medium Metro	-0.6	-3.5 (2017-2020)	0.008
Small Metro	-0.1	—	0.431
Micropolitan (Rural)	0.2	—	0.099
NonCore (Rural)	0.2	—	0.09

Note: A dash (—) indicates that no significant joinpoints APC was identified for the specified years in that location, implying stable mortality rates without notable changes.

Tumor-specific MHC class II upregulation associated with response to anti-PD-L1 therapy in patients with urothelial cancer.

İlayda Hasakioğulları, Mark Kockx, Bernadett Szabados, Matthew Young, Thomas Powles; CellCarta (Belgium), Antwerpen (Wilrijk), Belgium; CellCarta, Antwerp, Belgium; Barts Cancer Centre, Queen Mary University of London, London, United Kingdom; Barts Cancer Institute, London, United Kingdom

Background: The mechanism of response and resistance to immune checkpoint inhibition (ICI) remains to be defined in urothelial cancer. **Methods:** The abacus study explored neo-adjuvant atezolizumab prior to cystectomy in muscle-invasive bladder cancer (MIBC, NCT02662309). In this post hoc exploratory analysis, we utilized samples from the Abacus. Nanostring GeoMx Digital Spatial Profiler (DSP), a spatial transcriptomics platform enabling comprehensive characterization of the entire human transcriptome while preserving spatial information, was performed on Formalin Fixed Paraffin Embedded (FFPE) tissue from 12 paired biopsies (3 pCR, 3 MPR, and 6 relapse tumors). To guide region selection and tissue segmentation on the GeoMx DSP, we utilized SYTO 13, PanCK, CD45, and CD3 markers. Subsequently, we quantified the entire transcriptome in selected regions and conducted differential gene expression analysis using the DSP data analysis suite and BioTuring Lens platforms. **Results:** Tumor cells of the MPR samples showed upregulation of MHC class II genes (log2FC >1.52, $q < 5.5E-04$, $p< 9.7E-07$). pCR samples showed numerous tertiary lymphoid structures (TLS) in the remaining tumor bed. We then performed MHC class II (HLA-DR) immunohistochemistry staining to confirm this transcriptome-level finding on available FFPE samples from Abacus. The MPR response group (n=4) had significantly higher levels of MHC class II expression on tumor cells after the treatment than relapse (n=12) and stable disease (n=15) patients ($p < 0.001$). **Conclusions:** Upregulation of MHC class II on tumor cells in anti-PD-L1 responding patients is a novel finding. Together with the TLS presence, they offer insights into potential mechanisms underlying treatment response, thus aiding in identifying predictive biomarkers for ICI therapy in MIBC. Research Sponsor: CellCarta; Barts Cancer Institute.

Landscape analysis and oncologic outcomes in advanced urothelial carcinoma (UC) by NECTIN4 RNA expression.

Tyler F. Stewart, Sarah Elizabeth Fenton, Shayan Nazari, Andrew Elliott, Rohan Garje, Amirali Salmasi, Aditya Bagrodia, Chadi Nabhan, David James VanderWeele, Rana R. McKay; University of California, San Diego, Moores Cancer Center, La Jolla, CA; Northwestern University, Chicago, IL; Caris Life Sciences, Phoenix, AZ; Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Advanced UC is a devastating disease, however recent advances with antibody drug conjugates (ADCs), including enfortumab vedotin (EV), have improved outcomes significantly. Currently no biomarkers are clinically available to predict response to therapy. We hypothesized that benefit from EV may correlate with mRNA expression of NECTIN4, the gene encoding the relevant cell surface antigen for EV. Therefore, we performed a landscape analysis of NECTIN4 in advanced UC and correlated expression with oncologic outcomes. **Methods:** Bladder and upper tract UC samples were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or whole exome) and NovaSeq on RNA (whole transcriptome). UC samples were stratified by NECTIN4 mRNA levels into four quartiles. Tumor mutational burden (TMB) totaled somatic nonsynonymous mutations per tumor (high >10 mut/Mb). Insurance claims data were used to calculate survival outcomes using Kaplan-Meier estimates. Overall survival (OS) was calculated from the date of sample collection and date of treatment initiation to date of last follow up. Time on treatment (TOT) was calculated from date of treatment initiation to date of last treatment.Survival analysis was performed between top and bottom quartiles of NECTIN4 expression. **Results:** A total of 6,395 patient samples were analyzed [n=4335 from primary tumor (3496 bladder/urethra, 839 upper tract), n= 2060 from metastases]. Expression of NECTIN4 was associated with higher rates of mutations in FGFR3 (18.9% vs 6.9%), ERBB2 (11.8% vs 5.9%), pTERT (77.3% vs 62.6%), CCNE1 (5.6% vs 1.7%), SDHC (8.3% vs 0.6%) and with TMB-H status (46.2% vs 35.8%) but lower rates of TP53 mutations (54.6% vs 67.7%). NECTIN4 expression positively correlated with expression of TACSTD2 (TROP2), ERBB2 (HER2) and SLITRK6. Interestingly, NECTIN4 expression inversely correlated with PDL1 expression by IHC (22c3, 26.9% vs 59.2%). Similar findings were found when analysis was performed by primary bladder versus primary upper tract, as well as primary versus metastatic site. NECTIN4 expression was associated with longer OS in the overall population, and improvement in TOT (HR 0.53) and OS (HR 0.67) for patients treated with EV (Table). NECTIN4 expression was not associated with benefit with anti-PD1/L1 therapy. **Conclusions:** In the largest study investigating NECTIN4 expression in UC, we demonstrate co-expression of TACSTD2 (TROP2), ERBB2 (HER2) and SLITRK6 with NECTIN4. Expression of NECTIN4 correlated with favorable prognosis and predicted benefit from EV. NECTIN4 RNA expression could be a potential biomarker for selecting patients for treatment with EV. Further validation is required. Research Sponsor: None.

	Bottom Quartile NECTIN4	Top Quartile NECTIN4	HR
OS (N=1969)	13.8m	21.1m	0.76**
OS (Did not receive EV) (N=1561)	15.7m	22.1m	0.79**
TOT-EV (N=236)	2.7m	4.3m	0.53**
OS-EV (N=255)	12.9m	18.0m	0.67*

*P-value<0.05; **P-value <0.001

Updated interim analysis of a phase I/Ib study of enfortumab vedotin plus cabozantinib in patients with metastatic urothelial carcinoma.

Jacqueline T. Brown, Bassel Nazha, Yuan Liu, Kelsea Lozada, Jeremy D. Smith, Caitlin Hartman, Greta Russler McClintock, Omer Kucuk, Bradley Curtis Carthon, R. Donald Harvey, Mehmet Asim Bilen; Winship Cancer Institute of Emory University, Atlanta, GA; Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA

Background: Despite recent advances, metastatic urothelial carcinoma (mUC) remains a deadly disease. Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) specific for Nectin-4 approved in combination with pembrolizumab in 1L treatment and as monotherapy in later-line therapy. Cabozantinib (cabo) is a multi-tyrosine kinase inhibitor (TKI) that inhibits VEGF 1-3, MET and AXL with activity in heavily pretreated mUC. Preclinical data suggests anti-angiogenic agents may increase ADC penetration of tumor cells, potentially leading to therapeutic synergy. We report safety and preliminary efficacy data from the dose escalation and currently accruing dose expansion cohort of an ongoing phase I/Ib trial investigating cabo in combination with EV in patients (pts) with mUC. **Methods:** This is a phase I/Ib, open label, single arm trial at the Winship Cancer Institute of Emory University (NCT04878029). Pts with histologically confirmed mUC who received or were ineligible for platinum chemotherapy and a checkpoint inhibitor are eligible. The phase I dose escalation explored cabo 20 or 40 mg daily with standard dose EV (1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle) in 6 patients. Cabo 20 mg was chosen as the recommended dose for dose expansion and 4 patients have been treated to date. The primary endpoint is safety and tolerability of the combination. Key secondary objective is preliminary evidence of efficacy via objective response rate (ORR) per RECIST v1.1. **Results:** As of the 6 January 2024 data cut, 10 pts have been treated. All are male, 80% are white, and median age is 67.3 (49-85). Four pts were enrolled at the cabo 40 mg daily dose level in dose escalation and six pts have received cabo 20 mg daily in dose escalation and then expansion cohorts. The most common treatment-related AEs are fatigue (55.6%), skin rash, hand-foot syndrome, anorexia (all 44.4%), hyponatremia, hypophosphatemia, mucositis, ALT elevation, and peripheral sensory neuropathy (all 33.3%). Eight pts (88.9%) had a grade $\geq$ 3 treatment-related AE; the most common were neutropenia, hyponatremia, AKI and fatigue (all 22.2%). Of the 9 response-evaluable pts, the ORR was 88.9% with 7 responders achieving PR and 1 CR; the remaining 1 pt achieved SD with 18.94% target lesion reduction to date and remains on trial. The median target lesion reduction is 52.51% (18.94-100). Pts on cabo 40 mg and cabo 20 mg have a 100% and 60% dose reduction rate, respectively. **Conclusions:** This is the first clinical trial combining an ADC and TKI in mUC. These preliminary data suggest that the combination of EV and cabo is safe and tolerable with an AE profile consistent with that previously seen with each agent. Encouraging early evidence of activity has been observed. Enrollment of mUC pts into dose expansion with cabo 20 mg daily continues and further results including long-term outcomes and correlatives will be reported at a later date. Clinical trial information: NCT04878029. Research Sponsor: Exelixis.

4587 Poster Session

Longitudinal analysis of circulating tumor DNA in localized and metastatic urothelial cancer.

Adanma Ayanambakkam, Anh B. Lam, Niveditha Popuri, Laxmi Alekhya Mitta, Chao Xu, Sanjay Patel, Michael Cookson, Kelly Lynn Stratton, Minh Duc Phan, Shandy Gosnell, Amber Dawn Kraft Tarantini, Vineetha Finny, Jessica Elliott, Alicia Tyler-Dixon, Jessica Mayberry, Ryan David Nipp, Abdul Rafeh Naqash, Abhishek Tripathi, Rana R. McKay; Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK; University of Oklahoma Health Sciences Center, Oklahoma City, OK; University of Oklahoma College of Medicine, Oklahoma City, OK; Stephenson Cancer Center, Oklahoma City, OK; University of Oklahoma, Oklahoma City, OK; University of Oklahoma Health Sciences Center, Stephenson Cancer Center, Oklahoma City, OK; Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; University of California, San Diego Health, La Jolla, CA

Background: Circulating tumor DNA (ctDNA)-based minimal residual disease has been established as a prognostic biomarker in advanced urothelial carcinoma (UC). Despite the confirmed utility of ctDNA in muscle-invasive non-metastatic UC (nmUC), validation in patients with metastatic UC (mUC) remains unexplored. This study aims to prospectively assess the utility of ctDNA in nmUC and mUC **Methods:** This prospective study analyzed the results of longitudinal ctDNA testing in a single academic center of patients with UC. A personalized, tumor-informed, multiple PCR-NGS assay (Signatera, Natera, Inc) was used for the detection and quantification of ctDNA. A total of 203 samples were analyzed (median: 3 samples/patient) with a median follow up (mFU) from first ctDNA of 12months. nmUC and mUC patients with >1 ctDNA sample were included for analysis. Disease progression was assessed by clinical/radiographic exams. ctDNA dynamics were categorized based on clearance (ctDNA-), residual (ctDNA+), ≥50% quantitative reduction (≥50%ctDNAr), and <50% quantitative reduction (<50%ctDNAr), at any time point after treatment. We used Cox regression analysis to examine associations between ctDNA and the median time to progression (mTTP). **Results:** 67 patients (77% male, median age: 70 years,) with nmUC (n=31,46%) and mUC (n=36,54%) were included for analysis. Quantitative reduction in ctDNA samples aligned with radiographic responses in 98.5% (n=200) of samples analyzed. nmUC patients were treated with chemotherapy, immune checkpoint inhibitors (ICPI), and radiation. In nmUC, 74% (n=23) were ctDNA-, and all these patients remained progression free at the time of data analysis (mFU:13 months). Conversely, all ctDNA+ patients (n=8) experienced progression (mTTP:3 months). Among the 38.7% (n=12) of patients who pursued bladder preservation strategies, all ctDNA- patients (n=9) remained progression free (mFU:16 months), while all ctDNA+ patients (n=3) experienced progression (mTTP 3months). In mUC, patients were treated with chemotherapy, ICPI, and enfortumab vedotin. In mUC 86% (n=31) achieved ≥50%ctDNAr and 56% (n=20) achieved ctDNA- status. 23/31 (74%) patients with >50%ctDNAr remained progression free at analysis (mFU:11mo) and mTTP in 8/31 patients was 9.5months. Notably, 5/9 patients with ≥50%ctDNAr who underwent treatment breaks due to adverse events remained progression free (median treatment break: 7 months, mFU:19 months). Patients with ≥50%ctDNAr and ctDNA-had significantly improved mTTP when compared to patients with <50%ctDNAr (HR 0.18, p=0.02 and HR 0.11, p=0.009 respectively). **Conclusions:** Our findings underscore the potential for personalized assessment of tumor-informed ctDNA dynamics as a promising prognostic biomarker in patients with both localized and metastatic UC. Further prospective studies are necessary to validate utility for ctDNA guided treatment de-escalation in mUC. Research Sponsor: None.

FGFR3-mutated urothelial carcinoma of bladder and upper tract including ureter and renal pelvis: A comparative genomic profiling study.

Michael Basin, Rebecca A Sager, Dean Pavlick, Andrea Necchi, Philippe E. Spiess, Roger Li, Ashish M. Kamat, Petros Grivas, Liang Cheng, Douglas I. Lin, Jeffrey S. Ross, Gennady Bratslavsky, Joseph M Jacob, Shilpa Gupta, Neeraj Agarwal, Alina Basnet; SUNY Upstate Medical University, Syracuse, NY; Foundation Medicine, Inc., Cambridge, MA; Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, Milan, Italy; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Medicine, Division of Hematology/Oncology, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Warren Alpert Medical School of Brown University, Providence, RI; Department of Pathology, SUNY Upstate Medical University, Syracuse, NY; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Huntsman Cancer Institute, Salt Lake City, UT

Background: Activating DNA sequence genomic alterations (GA) in the *FGFR3* gene are known oncodrivers and relevant precision targets for patients with urothelial carcinoma. THOR-1 trial showed a significant overall survival benefit with erdafitinib (FGFR inhibitor) vs chemotherapy (taxane or vinflunine) in patients with advanced urothelial carcinoma of the bladder (UCB) or upper tract urothelial carcinoma (UTUC). PROOF-302 trial showed higher frequency of *FGFR3* GA in UTUC (30%) vs UCB (13%). We sought to explore differences in frequency of *FGFR3* alterations and the genomic landscapes of *FGFR3*-altered UCB, ureteral urothelial carcinoma (UUC) and renal pelvic urothelial carcinoma (RPUC). **Methods:** 10,798 UCB and 2,392 UTUC (871 UUC and 1521 RPUC) underwent hybrid capture-based comprehensive genomic profiling (CGP) to assess all classes of GA and measure MSI status, TMB level, genomic ancestry, genomic signature, germline mutations and HRD score. PD-L1 was determined by IHC Dako 22C3 using the TPS system. Results were compared using the Fisher Exact method with the Benjamini-Hochberg adjustment. **Results:** *FGFR3*mut+ status was significantly higher in RPUC (27.8%), followed by UUC (22.0%), and UCB (18.1%) (P<.0001) (Table). Patients with UCB were more often male compared to patients with UTUC. Median age, EUR ancestry, and GA/tumor were similar. "Targetable" GA in *ERBB2* (P=.03), *PIK3CA*(P=.05), KDM6A (P=.0009)were more frequent in *FGFR3*mut+ UCB vs *FGFR3*mut+ UTUC. Targetable GA in *PTEN*, *TSC1* and *MTAP* currently associated with drugs tested in trials were similar in UBC and UTUC. The KEGG ERBB and VEGF signaling pathways were more frequently identified in UCB (P=.036) and the MMR pathway more frequently identified in UTUC (P=.014). The HRD signature was similar in the groups. MSI-high status was significantly higher in UTUC vs UCB, but there was no significant difference in TMB or PD-L1 expression levels. **Conclusions:** Although histologically similar, the genomic landscape of *FGFR3*mut+ RPUC and UUC has notable differences with *FGFR3*mut+ UCB. Limitations include lack of clinical data annotation, inherent selection biases, and the retrospective nature of this work. Findings may impact clinical trial designs for UCB and UTUC, including evaluating combinations of anti-FGFR3 with other agents. CGP may also inform resistance mechanisms and putative biomarkers of response. Research Sponsor: None.

	***FGFR*mut+ UC**			**p-value**		
	Group 1 UCB (N=1954)	**Group 2 RPUC (N=423)**	**Group 3 UUC (N=192)**	**Group 1 vs 2**	**Group 1 vs 3**	**Group 1 vs 2 + 3**
ERBB2	7.4%	5.0%	2.6%	NS	0.0524	0.0291
MTAP	45.7%	44.5%	38.3%	NS	NS	NS
KDM6A	42.0%	37.8%	21.9%	NS	<0.0001	0.0009
PIK3CA	28.3%	24.1%	20.8%	NS	0.0986	0.0527
TERT	79.5%	73.1%	62.6%	0.0438	<0.0001	0.0001
TP53	31.6%	22.2%	38.5%	0.0043	NS	NS
MSI-high	1.7%	4.5%	6.9%	0.0242	0.0026	0.0001
Median TMB	5.2	5.0	5.0	NS	NS	NS
PD-L1 low positive	15.6%	30.8%	25.0%	NS	NS	NS

4589 Poster Session

Effect of antibiotic, proton pump inhibitor, H2 blocker, metformin and statin use on outcomes with immune checkpoint inhibitors (ICIs) in patients (pts) with metastatic urothelial carcinoma (mUC) in a real-world setting.

Charbel Hobeika, Scott Dawsey, Ubenthira Patgunarajah, David Lynn, Nikhil Pramod, Wei Wei, Monica Nair, Kimberly Maroli, Allison Martin, Moshe Chaim Ornstein, Christopher Eing Wee, Timothy D. Gilligan, Amanda Nizam, Amanda Bonham, Omar Y. Mian, Paul G. Pavicic Jr., C. Marcela Diaz-Montero, Shilpa Gupta; Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; John D. Dingell VA Hospital, Detroit, MI; Cleveland Clinic, Cleveland, OH; Cleveland Clinic Lerner College of Medicine, Cleveland, OH; Taussig Cancer Institute, Cleveland, OH; Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Cleveland Clinic Lerner Research Institute, Cleveland, OH

Background: Some reports suggest that concomitant medications like metformin (M) and statins (S) may enhance efficacy of ICIs in various solid tumors via immune remodeling. Meanwhile other drugs like antibiotics (Abx), proton-pump inhibitors (PPI), H2 blockers (H2b)—may negatively impact outcomes with ICI by affecting the gut microbiome. We report the effect (Abx), (PPI), (H2b), (M)and (S) in our larger cohort of mUC pts treated with ICI; atezolizumab (A), pembrolizumab (P), and maintenance Avelumab (Av). **Methods:** In our cohort of 474 pts with mUC treated with >/=2 cycles of ICI with A, P or Av between 2015 and 2023, we retrospectively reviewed the use of (Abx), (PPI), (H2b), (M) and (S) and their timing in relation to ICI start (within 60 or 30 days (d) prior to and after ICI start). Progression-free survival (PFS) and overall survival (OS) were calculated using Kaplan-Meier method, outcomes compared using log-rank testing and multivariate (MVA) Cox regression analysis. **Results:** Of 474 pts, 18.99% received A, 56.75% received P and 24.26% received Av. Median follow-up was 15.6 months. Survival data was available for 455 pts. On MVA Cox regression analysis, Abx use within 60 (d) before ICI start was associated with significantly worse OS while Abx use within 60 (d) post ICI start was associated with significantly worse PFS. PPI use was associated with significantly worse OS and PFS when used 60 (d) prior to ICI use. Metformin was associated with significantly worse PFS when used 60 days prior to ICI start and H2b and Sta did not have any effect on survival outcomes in our cohort. (Table) **Conclusions:** In our large cohort of pts with mUC treated with either A, P or Av, (Abx), (PPI) and (M) use 60 (d) prior to ICI start were associated with worse OS and PFS. These findings have the potential to influence clinical practice, considering a higher threshold for prescribing antibiotics or PPIs in mUC pts planned to start ICI. These findings warrant further validation in prospective trials. Research Sponsor: None.

Endpoint	Concomitant Medication	Hazard Ratio (HR, 95% CI)	P-value
OS	ABX within 60 days pre-IO	1.718 (1.3 – 2.2)	<.0001
	PPI within 60-day pre-IO	1.512 (1.1 – 2.0)	0.005
PFS	ABX within 60 days post-IO	1.391 (1.1 – 1.8)	0.01
	PPI within 60-day pre-IO	1.306 (1.0 – 1.7)	0.04
	Metformin within 60-day pre-IO	1.433 (1.0 – 2.1)	0.049

ERBB2 mutations and association with molecular phenotype in urothelial carcinoma.

Marc Machaalani, Talal El Zarif, Paul Stockhammer, Karl Semaan, Marc Eid, Razane El Hajj Chehade, Rashad Nawfal, Emre Yekeduz, Amin Nassar, Gwo-Shu Mary Lee, Sylvan C. Baca, Toni K. CHOUEIRI, Michael J Grant, Joaquim Bellmunt; Dana-Farber Cancer Institute, Boston, MA; Department of Internal Medicine, Yale University School of Medicine, New Haven, CT; Yale School of Medicine, New Haven, CT; Yale Cancer Center, New Haven, CT; Yale University, New Haven, CT

Background: Activating mutations (mut) in *ERBB2* are present in up to 11% of urothelial carcinoma (UC). *ERBB2*-targeted therapies have demonstrated encouraging results across multiple solid tumors. A better understanding of the mutational landscape of UC tumors harboring *ERBB2* mut is warranted to guide treatment selection. **Methods:** This study included patients (pts) with bladder or upper tract UC who had genomic tumor profiling data in the AACR Project GENIE database. *ERBB2*activating mut were confirmed using *OncoKB*, *PolyPhen*-2, or the available literature. The cohort was then stratified into pts with *ERBB2* mutantand *ERBB2* wild type tumors. Clinical characteristics and genomic data were compared between groups using Chi-squared and Mann–Whitney U tests. FDR-adjusted q-values were determined by the Benjamini–Hochberg method. **Results:** The cohort included 4,069 pts with UC, and most pts (n=3,475, 85%) had bladder UC. 376 (9.2%) pts had tumors harboring *ERBB2*-mutant UC. *ERBB2* mut were significantly enriched in pts with bladder vs. upper tract UC (9.6% vs. 6.7%, p=0.04) and in males vs. females (10.2% vs. 6.7%, p<0.001).The most common *ERBB2* mut were S310F/Y (51.4%) and I767M (6.6%) missense mut. A higher enrichment with extracellular domain *ERBB2*mut was observed in *ERBB2* mutant bladder vs. upper tract UC (66.2% vs. 41.5%, p<0.01), particularly for S310F/Y mut (55.5% vs. 36.6%, p=0.03). *ERBB2* mutant tumors had a distinct genomic phenotype characterized by a higher median tumor mutation burden (TMB) (15.6 vs 9.1 mut/Mb, p<0.0001), a lower rate of *FGFR3*co-mut, and a higher rate of co-mut in several genes (Table). Among *ERBB2* mutant tumors, the most common co-occurring amplifications occurred in *E2F3* (14.5%) and *ERBB2* (12.5%). *ERBB2* mutant tumors were more enriched with *ERBB2* amplifications vs. *ERBB2* wild type tumors (12.5% vs 5.2%, p<0.0001). Among *ERBB2* mutant tumors, those with vs. without concomitant *ERBB2* amplifications were associated with a higher frequency of co-occurring amplifications in *CDK12* (61.5% vs. 0%, p<0.0001), *RARA* (20% vs. 0%, p<0.0001), and *SUZ12* (12.5% vs. 0.72%, p<0.0001). **Conclusions:** This study provides deeper insights into the biology of UC tumors that harbor activating *ERBB2*mut. We demonstrate that tumors with activating *ERBB2* mut exhibit distinct molecular phenotypes characterized by higher TMB, lower frequency of *FGFR3* co-mutations, and higher frequency of co-occurring genomic alterations. These findings may help elucidate the patterns of response to *ERBB2*-targeted therapies and guide future combination therapy studies in UC. Research Sponsor: None.

Co-Mutation	*ERBB2*mutant UC % (n=376)	*ERBB2*wild Type UC % (n=3,693)	Q-value
FGFR3	8.8% (33)	22.9% (847)	<0.0001
ARID1A	38.2% (139)	23.7% (839)	<0.0001
KMT2A	21.6% (78)	9.6% (331)	<0.0001
ERCC2	19.6% (70)	9% (304)	<0.0001
ATM	18.6% (69)	10.5% (384)	<0.0001
NF1	15.6% (58)	6.2% (224)	<0.0001
BRCA1	11.1% (41)	4.7% (168)	<0.0001
CDK12	10.5% (35)	3.9% (126)	<0.0001

4591 Poster Session

Cost-effectiveness analysis of contemporary first-line (1L) agents in locally advanced/metastatic urothelial carcinoma (la/mUC).

Syed Arsalan Ahmed Naqvi, Kunwer Sufyan Faisal, Ammad Raina, Kaneez Zahra Rubab Khakwani, Zaryab Bin Riaz, Vishal S. Shah, Ewan Kemar Cobran, Parminder Singh, Syed A. Hussain, Alan Haruo Bryce, Irbaz Bin Riaz; Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ; Ziauddin Medical University, Karachi, Pakistan; Canyon Vista Medical Center, Sierra Vista, AZ; University of Arizona, Tucson, AZ; Rashid Latif Medical College, Lahore, Pakistan; Mayo Clinic, Phoenix, AZ; Mayo Clinic College of Medicine and Science, Scottsdale, AZ; University of Sheffield and Sheffield Teaching Hospitals, Sheffield, United Kingdom; City of Hope, Phoenix, AZ; Mayo Clinic, Scottsdale, AZ

Background: EV-302 and CheckMate 901 demonstrated significant survival benefit with enfortumab vedotin-pembrolizumab (EVPembro) and gemcitabine-cisplatin-nivolumab (GemCisNivo) as 1L therapy, respectively, in patients (pts) with la/mUC. However, whether these treatments are cost-effective or not remains unclear. **Methods:** A three-state Markov model (progression-free, progression and death) was developed. State utilities were derived from published literature. State transition probabilities were informed from point-probabilities and hazard ratios for OS and PFS obtained from the latest follow-up of eligible trials. Average sales price (2024 USD) for individual treatments (excluding ancillary charges) were obtained from the center of medicare and medicaid services (US payer's perspective). Treatment strategies were modeled in accordance with the dose/schedule reported in the eligible trials. Pts who received GemCis or Gem-carboplatin (GemCarbo) and did not progress were modeled to receive Avelumab maintenance. Half-cycle corrected costs and utilities were accrued over a 10-year lifetime horizon and were discounted at 3%. Monte Carlo simulation was used to estimate quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs). A willingness-to-pay threshold (WTP) of 100,000$ per QALY was used. **Results:** In cisplatin-eligible pts, GemCisNivo demonstrated a 0.8 QALY gain over GemCis at an ICER of 21,127 ($/QALY). GemCisNivo was also associated with an incremental net monetary benefit (INMB) of 63,099$ relative to GemCis. EVPembro demonstrated a 2.4 QALY gain over GemCis at an ICER of 915,283 and a 1.6 QALY gain over GemCisNivo at an ICER of 1,406,308. In cisplatin-ineligible pts, EVPembro demonstrated a 2.4 QALY gain over Gem-carboplatin (GemCarbo) at an ICER of 934,761. Price threshold analyses demonstrated that EVPembro is likely to be cost-effective at a cost of 12,344$ for cisplatin-eligible and 13,374$ per cycle for cisplatin-ineligible pts (original cost: 35,665.60$ per cycle). Sensitivity analysis using a total of 12 cycles for EVPembro showed cost-effectiveness at an ICER of 69,594 relative to GemCisNivo in cisplatin-eligible pts, and at an ICER of 53,099 relative to GemCarbo in cisplatin-ineligible pts. **Conclusions:** In terms of US payer's perspective, GemCisNivo is most likely to be cost-effective in cisplatin-eligible pts at the WTP of 100,000 $/QALY. Limiting the number of cycles for EVPembro may render it as a cost-effective 1L treatment in la/mUC pts regardless of cisplatin-eligibility status. Research Sponsor: None.

Efficacy and safety of atezolizumab concurrent with radiotherapy in patients with muscle-invasive bladder cancer: An interim analysis of the atezobladderpreserve phase II trial (SOGUG-2017-A-IEC(VEJ)-4).

Ovidio Fernandez Calvo, Teresa Bonfill, Francisca Martinez Madueño, Nuria Romero-Laorden, Silvia Sequero-Lopez, Montserrat Domenech-Santasusana, Elena Sevillano, José García Sánchez, Pilar Canoa Román, Carlos Álvarez-Fernández, Sergio Vazquez-Estevez; Medical Oncology Department-Complejo Hospitalario Universitario de Ourense, Ourense, Spain; Hospital Universitari Parc Taulí, Sabadell, Spain; HU Sant Joan de Reus, Reus, Spain; Hospital Universitario de la Princesa, Madrid, Spain; Hospital Universitario San Cecilio, Granada, Spain; Medical Oncology Department, Fundació Althaia, Barcelona, Spain, Manresa, Spain; HM Sanchinarro Centro Integral Oncologico Clara Campal (CIOCC), Madrid, Spain; Hospital Arnau Vilanova Valencia, Valencia, Spain; Hospital Universitario Lucus Augusti, Lugo, Spain; Medical Oncology Department, Hospital Universitario Central de Asturias, Oviedo, Spain; Hospital Universitario Lucus Augusti (HULA), EOXI de Lugo, Cervo e Monforte, Lugo, Spain

Background: Combined-modality treatments (CMTs) are bladder-preserving alternatives for patients (pts) ineligible for radical cystectomy. CMTs combine maximal transurethral resection (TUR) of bladder tumor, radiotherapy (RT), and chemotherapy. Emerging immune therapies seem to enhance RT-induced tumor-specific immune response. RT combined with anti-PD-1/PD-L1 therapy shows promising efficacy with acceptable toxicity. This ongoing study evaluates the efficacy and safety of atezolizumab (ATZ) concurrent with external beam RT (EBRT) for muscle-invasive bladder cancer (MIBC) treatment as bladder preservation therapy. Here, we present an interim analysis. **Methods:** Open, multicenter, phase II trial in adults with MIBC in clinical stages cT2-T4a N0 M0 not candidates for radical cystectomy. Treatment involves 6 doses of ATZ (1200 mg IV/3 weeks) from day 1 of EBRT and 60 Gy of RT in 30 fractions over 6 weeks at 2 Gy/day. The primary endpoint is pathological complete response (pCR), a grade 5 response per Miller and Payne criteria, 1-2 months after ATZ last dose. An interim analysis (data cut-off: Oct. 2023) of the primary endpoint encompassing data from the screening to the safety visits has been conducted. Adverse events (AE) and serious AE (SAE) incidence has been secondarily assessed. **Results:** From Sep. 2019 to Oct. 2023, 59 pts were screened; 20 were excluded for non-compliance with eligibility criteria (15 pts), consent withdrawal (6 pts), and AE (1 pt). Evaluable population consisted of 39 pts. Median age was 79.7 years. Most patients had clinical stages T2a (61.5%) and T2b (25.6%). 37 (94.9%) pts had at least one previous clinically significant condition, 24 (61.5%) had prior surgery, and 39 (100%) were receiving concomitant medication. TUR was performed in 23 (71.9%) pts. All 26 (100%) pts with pathological assessment at safety visit achieved pCR; none underwent cystectomy. 37 (94.9%) pts experienced AEs (23 [59.0%] pts grade 1 AE, 13 [33.3%] pts grade 3, and 1 [2.6%] pt grade 3), with asthenia (21 pts) and diarrhea (17 pts) being most common. AEs related to EBRT occurred in 24 (61.5%) pts; those related to ATZ in 21 (53.8%). 13 (33.3%) pts had at least one SAE (including renal failure in 3 pts and hepatotoxicity in one). One (2.6%) pt had at least one SAE related to EBRT and 3 (7.7%) pts SAEs related to ATZ. AEs leading to treatment discontinuation occurred in one (2.6%) pt and AEs leading to death in 2 (5.1%), in one of them related to treatment. **Conclusions:** Interim results suggest that ATZ combined with EBRT seems to be effective in achieving pCR in a vulnerable elderly population with multiple comorbidities. The safety profile appears manageable. The final analysis of this study will provide valuable insights into the effect of ATZ with EBRT on clinical outcomes, such as survival, in addition to updated safety data. Clinical trial information: NCT04186013. Research Sponsor: Roche Farma, SA.

Clinical efficacy and biomarker analysis of pre-operative ipilimumab plus nivolumab in stage III urothelial cancer: The NABUCCO trial update.

Chantal Stockem, Alberto Gil Jimenez, Jeroen van Dorp, Nick Van Dijk, Maurits L van Montfoort, Maartje Alkemade, Iris M. Seignette, Annegien Broeks, Erik Hooijberg, Wim Brugman, Laura Mertens, Bas W.G. van Rhijn, Jeantine M De Feijter, Toine van der Heijden, Niven Mehra, Richard P. Meijer, Britt Suelmann, Daniel J Vis, Lodewyk F.A. Wessels, Michiel Simon Van Der Heijden; Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Molecular Carcinogenesis, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands; Core Facility of Molecular Pathology and Biobanking, The Netherlands Cancer Institute, Amsterdam, Netherlands; Core Facility Molecular Pathology and Biobanking, Netherlands Cancer Institute, Amsterdam, Netherlands; Genomics Core Facility, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Surgical Oncology (Urology), Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Urology, Radboud University Medical Center, Nijmegen, Netherlands; Radboud University Medical Center, Nijmegen, Netherlands; Department of Oncological Urology, University Medical Center Utrecht, Utrecht, Netherlands; Department of Medical Oncology, University Medical Center Utrecht, Utrecht, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands

Background: In the NABUCCO trial, pre-operative ipilimumab (ipi) + nivolumab (nivo) was studied in patients (pts) with stage III (cT3-4aN0M0 or cT1-4aN1-3M0) urothelial cancer (UC). In cohort 1 (C1), 11/24 pts (46%) achieved complete pathological response (ypT0N0). In cohort 2 (C2), two ipi/nivo dosing regimens were studied in 30 additional pts. The results suggest that a higher ipi dosage (3 mg/kg) is more effective in stage III UC. Here, we present an update on clinical efficacy and an exploratory biomarker analysis. **Methods:** In NABUCCO, UC pts received sequential ipi 3 + nivo 1 (ipi-high, C1; n=24) and combined ipi 3 + nivo 1 (ipi-high, C2A; n=15) or ipi 1 + nivo 3 (ipi-low, C2B; n=15), followed by radical cystectomy. The cut-off date for the updated survival analysis was March 31th, 2023. Whole exome sequencing was performed on pre-treatment formalin-fixed paraffin-embedded (FFPE) tumor tissue and peripheral blood to call somatic variants. RNA from pre- and post-treatment FFPE tissue was isolated and sequenced. PD-L1 immunohistochemistry (clone 22C3) was performed on baseline FFPE tumor tissue and manually scored using the combined positivity score (CPS), tumor positivity score (TPS), and immune score (IC). To profile the tumor microenvironment, pre- and post-treatment FFPE slides were stained with three multiplex immunofluorescence (mIF) panels consisting of antibodies against CD3, CD20, FoxP3, PanCK, CD68, CD206, IRF8, CD8, CD103, and TCF1. Tumor areas were annotated manually and distinguished from stromal areas using a classifier and tissue segmentation. **Results:** After a median follow-up of 48 months, 2-year overall survival (OS) was 90% upon ipi-high (C1+2A) and 73% upon ipi-low (C2B). Progression-free survival (PFS) at 2 years was 75% upon ipi-high (C1+2A) and 67% upon ipi-low (C2B). Tumor mutational burden (TMB) was higher in responding pts (≤ypT1N0) across treatment arms (p=0.00068). Treatment response was associated with PD-L1 positivity (CPS p=0.048; TPS p=0.004; IC p=0.016). Increased RNA expression of immune-related genes such as IDO1, CTLA4, and PD-L1, and signatures of T-helper 1- and T-follicular helper cells at baseline were associated with response in pts treated in the ipi-low arm, but not in the ipi-high arms. Increased baseline RNA expression of a TGFβ signature was associated with non-response. Nonresponders to ipi/nivo demonstrated enhanced RNA expression of CD8 T-cell and stromal signatures. Pending results of the mIF analysis will be presented at ASCO 2024. **Conclusions:** Both OS and PFS at 2 years were numerically better in UC pts treated with a high ipi dose. Overall, TMB and PD-L1 positivity were associated with treatment response regardless of ipi dose. Pre-existing intratumoral T-cell immunity appeared to be required to induce an anti-tumor response in UC pts treated with ipi-low. Clinical trial information: NCT03387761. Research Sponsor: BMS.

Phase II trial of intravesical camrelizumab in BCG-unresponsive high-risk non-muscle invasive bladder cancer.

Yijun Shen, Liangju Peng, Peihang Xu, Yanhao Wang, Xiang Wang, Yao Xudong, Yushan Liu, Ding-Wei Ye; Fudan University Shanghai Cancer Center, Shanghai, China; Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Shanghai Tenth People's Hospital, Tong Ji University, Shanghai, China; Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: In a phase I study, intravesical camrelizumab (at a maximum tolerated dose [MTD] of 200 mg) was well tolerated by patients with BCG-unresponsive high-risk non-muscle invasive bladder cancer (NMIBC). This phase II trial aimed to assess the efficacy and safety of intravesical camrelizumab at the established phase I MTD. **Methods:** Patients with histologically confirmed BCG-unresponsive high-risk NMIBC, who were ineligible for or declined radical cystectomy, received intravesical camrelizumab at a dose of 200 mg every week for up to 6 weeks as the induction course. Subsequently, the maintenance therapy started with 200 mg administered every 3 weeks and continued until reaching the maximum treatment duration of 2 years or in the event of disease progression or unacceptable toxicity. The primary endpoint was the 3-month event-free survival (EFS) rate. The secondary endpoints included 6-month EFS rate, 1-year EFS rate, recurrence-free survival (RFS), progression-free survival (PFS), and safety. Biomarker exploration included PD-L1 expression and protein sequencing. **Results:** Between June 2021, and December 2023, 14 patients were enrolled and received at least one dose of camrelizumab, all of whom were included in the safety analysis.At a median follow-up of 23.1 months (IQR 15.8-28.6), the median EFS was 12.68 months (95% CI 6.31-NE), with a 3-month EFS rate of 92.3% (95%CI 77.8-100), a 6-month EFS rate of 75.5% (95%CI 51.4-99.7) and a 12-month EFS rate of 50.3% (95%CI 22.1-78.6). Both median RFS and PFS was 12.68 months (95% CI 6.31-NE). Grade $\geq$ 3 treatment-emergent adverse events (TEAEs) occurred in 2 (14.3%) patients, one with urinary tract infection and the other with vertebrobasilar insufficiency. Serious TEAEs occurred in one (7.1%) patient. No deaths were reported. PD-L1 expression was not related to treatment efficacy. Protein sequencing revealed a total of 296 proteins with differential expression between responsive and unresponsive patients. Analysis using Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway demonstrated that the responsive group was associated with activated biological processes, including T cell receptor signaling pathway, alpha-beta T cell activation, and adaptive immune response. **Conclusions:** Intravesical camrelizumab demonstrated promising anti-tumor activity and acceptable tolerance in patients with BCG-unresponsive NMIBC who either declined or were ineligible for radical cystectomy. This suggests its potential as an effective non-surgical and topical treatment option for this specific population. The efficacy was attributed to enhanced immune pathway activation. Clinical trial information: NCT04706598. Research Sponsor: None.

4595 Poster Session

Combined high-resolution H3K27ac epigenomic and single-cell transcriptional profiling as a signature predictive of response to neoadjuvant immune checkpoint inhibitors (ICI) in urothelial cancer (UC).

Joaquim Bellmunt, Margot Hully, Ilana B. Epstein, Sonsoles Liria, Yingtian Xie, Miguel Muñoz, Paula Garoz, Nuria Fernandez, Oscar Buisán, Toni K. CHOUEIRI, Cecilia Cabrera, Henry Long, Paloma Cejas; Dana-Farber Cancer Institute, Boston, MA; CFCE - Dana-Farber Cancer Institute, Boston, MA; Servicio de Urología, Hospital Universitario de Bellvitge, Barcelona, Spain; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Irsicaixa - IGTP - Badalona, Badalona, Spain; CFCE, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Multiple molecular predictors have been associated with response to ICI in metastatic UC (mUC), including clonal TMB, APOBEC mutagenesis and multiple RNA signatures. Tumor-intrinsic and tumor-extrinsic (microenvironmental) properties can drive resistance to PD-1/PD-L1 inhibitors, although the factors that determine resistance specifically in MIBC remains incompletely characterized. Epigenomic analysis combined with single cell (sc) technology can reveal mechanisms of response involving both cancer cells and the microenvironment. **Methods:** We identified two MIBC patients' cohorts from Dana-Farber Cancer Institute (DFCI) and from Hospital Trias i Pujol in Spain treated with neoadjuvant therapy with ICI with tissue available pre- and post- treatment. Molecular profiling was performed with H3K27ac in Formalin-Fixed Paraffin-Embedded (FFPE) blocks and scRNAseq from Fresh Frozen (FF) and FFPE tissues. For the analysis, we performed peak calling, unsupervised analysis (using our internal pipeline), comparison of enhancers with a published datasets (using Cistrome toolkit) and sc analysis using Seurat. **Results:** 35 patients with pre and post available samples were included in the analysis. The H3K27ac enhancer analysis revealed a signature predictive of treatment response to immunotherapy. Comparison with publicly available ChIP-seq datasets showed that enhancers more active in pre-treatment samples in responders were highly represented in lymphoid lineages. In contrast, the enhancers less active in responders were associated with squamous differentiation. When translated to a gene expression signature, we found enhancers at novel and known genes described in UC that included *CYTOR, TGFBR2* and *IKZF1(*involved in immunotherapy response) and *FYN, PDE4B* and *GPR174* involved in cell migration, microenvironment and EMT among the top ten genes. We projected the gene signature over a scRNAseq atlas resulting from 20 patients that includes all inflammatory lineages, and found an increase within specific T cell populations and a reduction of B and plasma cells in responders as compared to non-responders in the pre-treatment samples. **Conclusions:** Our combined epigenetic and scRNAseq strategy revealed the existence of specific microenvironment and tumor states in pre-treatment samples from MIBC. We also provided a novel gene signature predictive of response. Prospective validation is ongoing. Research Sponsor: None.

A phase II clinical trial of toripalimab combined with cisplatin plus gemcitabine chemotherapy as neoadjuvant treatment for muscle-invasive bladder cancer.

Rong Yang, Tianhang Li, Shun Zhang, Shiwei Zhang, Hongqian Guo; Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China; Department of Urology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University; Institute of Urology, Nanjing University, Nanjing, China; Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China

Background: Recently clinical trials like BLASST-1 and SAKK06/17 showed that immunotherapy combined with chemotherapy as neoadjuvant regimen of muscle-invasive bladder cancer (MIBC)may produce synergistic effects with good tolerability. Toripalimab, a PD-1 inhibitor, has achieved good therapeutic effects in advanced urothelial cancer. This clinical study was designed to verify the safety and efficacy of Toripalimab with gemcitabine-cisplatin (GC) as neoadjuvant therapy (NAT) for MIBC. **Methods:** It is a prospective, single-arm, open-label, single-center phase II clinical study from China (ChiCTR2100051298). Thirty patients with MIBC clinically staged as T_{2-3b} N_0 M_0, who were scheduled for RC were enrolled. Patients received: Toripalimab 240 mg + Gemcitabine 1000 mg/m^2 + Cisplatin 70mg/m^2 on day 1, Gemcitabine 1000mg/m^2 on day 8 every 21 days (1 cycle), totally for 4 cycles. RC will be performed 1 month after last therapy. The primary endpoint is pathological complete response (pCR), and the secondary endpoints are safety, overall survival (OS), and progression-free survival (PFS). The tumor regression effect after NAT will be evaluated by comparing the postoperative pathological results with the preoperative radiological results. The FISHER's exact test was used to analyze the relationship between genomic changes / tumor mutation burden (TMB) and pCR rate. This study has been approved by the Ethics Committee of Gulou Hospital, Nanjing. **Results:** From Jan 2020 to Dec 2021, 30 individuals participated in the study and received at least 1 cycle therapy, and 3 dropped out before RC. Among the patients who underwent RC, the pathological response (PaR) rate was 63% (17/27) and the pCR rate was 40.7% (11/27). The 1-year and 3-year PFS rates are 85.2% and 77.6%, respectively; The 1-year and 3-year OS rates are 96.2% and 84.6%, respectively. In the patients with PD-L1 expression $\geq$5% (n = 16), pCR and PaR rates was 43.8% (7/16) and 68.8% (11/16), respectively. In the patients with PD-L1 expression $<$ 5% (n = 11), the pCR rate was 36.4% (4/11) and the PaR rate was 63.6% (7/11). The status of PD-L1 expression and TMB were not associated with pCR rate. Further biomarker analysis indicated that patients with any dual co-mutation in KMT2D/ERBB2/EPHA2 were associated with a lower pCR rate. Among the 30 patients, 24 cases (80%) experienced treatment related adverse reactions (AEs), with no grade 4 AEs nor above. Two patients experienced grade 3 AEs, including thrombocytopenia (1) and proteinuria (1). The most common AEs were pruritus (33.3%), fatigue (26.7%), and nausea (23.3%). Nine cases (30%) experienced immune-related AEs, including rash, thyroid dysfunction, increased blood glucose, and pneumonia, with no grade 3-4 AEs. **Conclusions:** Toripalimab combined with GC chemotherapy demonstrates good efficacy and tolerability and is an alternative option for NAT of MIBC. Clinical trial information: ChiCTR2100051298. Research Sponsor: None.

4597 Poster Session

Outcomes of patients with bacillus Calmette-Guérin–unresponsive high-risk non–muscle-invasive bladder cancer who demonstrated nonresponse to pembrolizumab in KEYNOTE-057: A post hoc analysis.

Roger Li, Joshua Linscott, Girish S. Kulkarni, Andrea Necchi, Mathieu Roumiguié, Eric A. Singer, Edward M. Uchio, Joost L Boormans, Aiwen Xing, Margot Van den Sigtenhorst, Ekta Kapadia, Ashish M. Kamat; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University Health Network, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, Milan, Italy; IUCT-Oncopole, Toulouse, France; The Ohio State University Comprehensive Cancer Center, Columbus, OH; UCI Health, Orange, CA; Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands; Merck & Co., Inc., Rahway, NJ; MSD Netherlands, Haarlem, Netherlands; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The phase 2 KEYNOTE-057 trial (NCT02625961) demonstrated that pembrolizumab can serve as a bladder-sparing option for patients (pts) with high-risk non–muscle-invasive bladder cancer (NMIBC) who are unresponsive to bacillus Calmette-Guérin (BCG) and are unable or unwilling to undergo radical cystectomy (RC). However, the outcomes (especially related to progressive disease [PD]) of pts who do not respond to bladder-sparing therapies (BSTs), including pembrolizumab, are of concern. We conducted a post hoc analysis of the KEYNOTE-057 trial to assess the clinical outcomes of pts who experienced persistent or recurrent high-risk NMIBC despite pembrolizumab therapy and subsequently received either RC or other BST. **Methods:** Pts with BCG-unresponsive carcinoma in situ (CIS) and/or papillary-only tumors who had nonresponse (persistent or recurrent high-risk NMIBC) to pembrolizumab were evaluated in the following groups: (1) pts who received upfront RC (≤4 mo of treatment failure confirmation); (2) pts who received delayed RC (>4 mo after treatment failure or received other BST before RC); and (3) pts who received BST alone (received BST alone or no reported subsequent treatment). Analyses included PFS (lack of development of muscle-invasive bladder cancer [MIBC] or metastatic disease or death due to PD) and OS, indexed from the date of pembrolizumab nonresponse. Pts with upfront RC found to have upstaging to MIBC (due to initial understaging) were excluded from the PFS analysis unless they developed subsequent PD. Pathologic outcomes in pts undergoing upfront vs delayed RC were also evaluated. **Results:** Of the 144 pts who were nonresponders to pembrolizumab, 39 underwent upfront RC, 33 underwent delayed RC, and 72 underwent BST alone. Of pts who underwent upfront RC, the pathologic stages were T0, 26%; NMIBC (Ta, T1, CIS), 64%; and MIBC (T2, T3, T4), 10%. Of pts who underwent delayed RC, the pathologic stages were T0, 15%; NMIBC, 67%; and MIBC, 15%. Median time from pembrolizumab nonresponse to data cutoffs (cohort A: May 30, 2023; cohort B: Oct 20, 2022) was 59.7 mo (range, 10.9-80.7). Median PFS was not reached across all 3 groups. The 36-mo PFS rates were 78% (95% CI, 60-89) for upfront RC, 68% (95% CI, 49-82) for delayed RC, and 86% (95% CI, 74-92) for BST alone. Median OS was not reached across all 3 groups. **Conclusions:** Oncologic outcomes were similar between pts treated with BST or RC following nonresponse to pembrolizumab. Pts who underwent upfront vs delayed RC had similar pathologic outcomes. Data from this analysis suggest that pts were not harmed by BST following pembrolizumab and that a window of safety may exist for implementing second-line BST prior to RC. Clinical trial information: NCT02625961. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Cost effectiveness analysis of nadofaragene firadenovec for the treatment of high-risk, bacillus Calmette-Guerin–unresponsive, non-muscle invasive bladder cancer from a US third-party payer perspective.

Min Yang, Xinglei Chai, Ashton Moradi, Dongni Ye, Angela Zhao, Amy Guo, Yair Lotan; Analysis Group, Boston, MA; Analysis Group Inc., Boston, MA; Ferring Pharmaceuticals, Parsippany, NJ; Department of Urology, University of Texas Southwestern, Dallas, TX

Background: Bladder cancer is the second most common cancer in the urinary tract in the United States (US), with 75% restricted to the superficial layers of the bladder and termed as non-muscle invasive bladder cancer (NMIBC). Bacillus Calmette-Guerin (BCG) is the standard of care for high risk NMIBC patients; however, bladder preserving treatments are limited after BCG failure. Nadofaragene firadenovec, an interferon-alfa-2b encoding gene therapy, is approved for the treatment of high-risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) with or without papillary tumors (CIS ± Ta/T1). This study assessed cost-effectiveness of nadofaragene firadenovec compared to pembrolizumab from a US third-party payer perspective. **Methods:** A Markov model was developed to estimate total costs, quality-adjusted life-years (QALYs), and corresponding incremental cost per QALY ratios (ICER) over a lifetime time horizon for patients treated with nadofaragene firadenovec or pembrolizumab. In the absence of head-to-head data comparing nadofaragene firadenovec to pembrolizumab, the model population was based on Phase 3 trial for nadofaragene firadenovec (NCT02773849, data cut: July 8, 2019) and included adult patients (mean age of 71.0 years; 11.7% female) with high-risk, BCG unresponsive NMIBC with CIS ± Ta/T1. Pembrolizumab data was informed by the published KeyNote-057 trial (NCT02625961, data-cut: May 25, 2020). The model consisted of 7 mutually exclusive health states with a three-month model cycle: NMIBC disease-free, NMIBC recurrence, MIBC, metastatic disease, cystectomy, post-cystectomy, and death. Drug costs, adverse events (AEs) costs, and health state associated medical costs were included and discounted at 3% annually. The nadofaragene firadenovec and pembrolizumab prices were informed by 2023 U.S. pricing compendia. Sensitivity analyses were performed. **Results:** Compared to pembrolizumab, nadofaragene firadenovec resulted in an ICER of $123,725 per QALY gained. The incremental cost was $24,194 (nadofaragene firadenovec: $374,280; pembrolizumab: $350,086) and the incremental QALYs were 0.196 (nadofaragene firadenovec: 4.560; pembrolizumab: 4.364). The cumulative drug acquisition and administration costs for nadofaragene firadenovec and pembrolizumab were $181,134 and $141,954 respectively, and AE costs were $248 and $2,749 and medical costs associated with health states were $192,898 and $205,382, respectively. The ICERs for nadofaragene firadenovec remained cost-effective across a majority of the sensitivity analyses and simulations. **Conclusions:** The analysis suggests that nadofaragene firadenovec is cost-effective compared to pembrolizumab for the treatment of high-risk, BCG unresponsive NMIBC with CIS ± Ta/T1 at a willingness to pay of $150,000/QALY. Research Sponsor: Ferring Pharmaceuticals.

A multi-institutional observer study of AI-aided oncologists' performance on treatment response assessment of bladder cancer.

Monika Joshi, Di Sun, Ajjai Shivaram Alva, Philip Palmbos, Yousef Zakharia, Rohan Garje, Heang-Ping Chan, Richard H. Cohan, Lubomir Hadjiiski; Penn State Cancer Institute, Hershey, PA; University of Michigan, Ann Arbor, MI; Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI; University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA; Department of Internal Medicine, Division of Hematology/Oncology, University of Iowa, Iowa City, IA; University of Michigan Medical School, Ann Arbor, MI

Background: Neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC) results in a complete response of 30-40%. The remaining patients who do not benefit from this approach are at risk for disease progression prior to RC. Prompt accurate treatment response assessment (TRA) of NAC prior to RC is crucial to guide treatment and minimize toxicity. Our study evaluated the impact of artificial intelligence (AI)-based decision support system (CDSS-T) on oncologists' performance in identifying patients who respond completely (stage T0) to NAC. **Methods:** We conducted a multicenter retrospective-observational study. The pathological cancer stage after NAC f/u RC served as the reference standard. CT Urograms (CTU) of 123 patients were collected, with a total of 157 evaluable imaging pairs including pre- and post-NAC CTU (N of T0=40). Five oncologists from 3 institutions participated. We randomly selected 51 CTU pairs for each oncologist, and each one read the set of 51 cases twice with a washout period of 3 weeks to eliminate reading memory. Each reading session included sequential reading without and then with the aid of CDSS-T. The CDSS-T was developed by combining radiomics and deep-learning AI predictions. Inter-observer performance was analyzed by the ROC iMRMC method, and intra-observer performance measured by Krippendorff's alpha (agreement: α) and Bland–Altman (variability: standard deviation (SD)) methods. **Results:** With CDSS-T aid, the 5 oncologists had a higher mean area under the curve (AUC) and smaller SD for both first readings (0.77±0.08 without, 0.86±0.07 with CDSS-T) and second readings (0.77±0.09 without, 0.84±0.04 with CDSS-T). With aid they also had higher intra-observer agreement (α: 0.70±0.05 without, 0.84±0.04 with CDSS-T) and smaller intra-observer variability (SD: 26.28±2.69 without, 19.75±2.86 with CDSS-T). **Conclusions:** CDSS-T improves oncologists' accuracy in TRA, increases intra-observer agreement, and reduces intra-observer variability. A prospective study is ongoing in MIBC to validate the findings. Research Sponsor: None.

	Reading 1 (AUC)		Reading 2 (AUC)		Intra-observer agreement α		Intra-observer variability SD	
Oncologists	w/o CDSS-T	w/ CDSS-T	w/o CDSS-T	w/ CDSS-T	w/o CDSS-T	w/ CDSS-T	w/o CDSS-T	w/ CDSS-T
#1	0.65	0.75	0.73	0.78	0.69	0.83	30.46	21.57
#2	0.81	0.85	0.82	0.87	0.64	0.80	26.08	19.07
#3	0.81	0.89	0.77	0.83	0.73	0.85	26.05	18.67
#4	0.73	0.88	0.64	0.83	0.69	0.89	22.92	16.01
#5	0.86	0.93	0.87	0.87	0.77	0.80	25.91	23.45
Mean±SD	0.77±0.08	0.86±0.07	0.77±0.09	0.84±0.04	0.70±0.05	0.84±0.04	26.28±2.69	19.75±2.86

Tumor fraction and copy number burden from urinary cell-free tumor DNA (utDNA) to predict minimal residual disease prior to repeat-transurethral resection in high-risk non-muscle invasive bladder cancer (HR-NMIBC).

Joshua Linscott, Hiroko Miyagi, Billie Gould, Prithvi Murthy, Kyle M Rose, Lucia P Camperlengo, Giancarlo Bonora, Logan Zemp, Scott Michael Gilbert, Philippe E. Spiess, Wade J. Sexton, Joshua J Meeks, Pan Du, Shidong Jia, Roger Li; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Predicine, Inc., Hayward, CA; Oschner Medical Center, Jefferson, LA; Predicine, Hayward, CA; Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Northwestern University, Department of Urology, Feinberg School of Medicine, Chicago, IL

Background: Genomic alterations detected in urinary cell-free tumor DNA (utDNA) are concordant with those from tissue samples in patients with urothelial carcinoma. In this prospective study, we demonstrate that utDNA alterations and copy number variation can be used to detect minimal residual disease (MRD) prior to standard-of-care repeat transurethral resection of bladder tumors (rTURBT) in patients with high risk non-muscle invasive bladder cancer (HR-NMIBC). **Methods:** A total of 53 patients with high-risk NMIBC were enrolled prior to rTURBT. PredicineWES+ whole exome sequencing with boosted 600+ oncogene coverage was performed on the index TURBT (iTURBT) tissue. Urine samples were collected immediately prior to rTURBT (preUR). Low Pass Whole Genome Sequencing (LP-WGS) was used to detect utDNA and estimate copy number burden (CNB). Tumor fraction (tf) detected in utDNA was measured using PredicineBEACON personalized ultra-deep sequencing MRD probes designed from somatic variants detected in iTURBT tissue. MRD probes leverage up to 60 patient-specific alterations and a fixed 500 gene hotspot panel. Analysis included receiver operator curves (ROC) to establish CNB and tf efficacy in detecting residual cancer, based on the pathological findings from rTURBT. Specific thresholds for test positivity were set from ROC analysis and used to evaluate performance characteristics of CNB and tf separately and then in step-wise model. **Results:** In this HR-NMIBC cohort, residual disease was detected in 36/53 pts (68%) on pathologic evaluation. Using the CNB score from preUR samples, residual disease was detected with an overall AUC of 0.86. Setting the CNB threshold >6.1 yielded a positive likelihood ratio of 11.7 and negative likelihood ratio of 0.37 for detecting MRD. For patients with personalized urinary tf (n=34), a receiver operator curve demonstrated an area under the curve (AUC) of 0.89. Median urinary tf was 3.5% for patients with MRD vs. <0.05% (undetectable) for disease-free patients ($p<0.001$). Best thresholds for MRD detection per Youden's index were tf >=6.8% and CNB >6.1. When combined into a step-wise model, the two assays together led to improved performance with 85.7% sensitivity, 100.0% specificity and an overall accuracy of 91.4%. **Conclusions:** Minimal residual disease can be detected using utDNA prior to rTURBT with high accuracy, making this a promising urinary biomarker. If validated, the combined approach using CNB and tf from utDNA for the detection of MRD can be used to predict patients in need of maximal resection prior to starting intravesical therapy. Research Sponsor: None.

Final results of CORE-001: A phase-2, single arm study of cretostimogene grenadenorepvec in combination with pembrolizumab in patients with BCG-unresponsive, non-muscle invasive bladder cancer with carcinoma in situ.

Roger Li, Paras H Shah, Tyler F. Stewart, Trinity Bivalacqua, Donald L. Lamm, Daniel M. Geynisman, Joshua J Meeks, Edward M. Uchio, Joseph M Jacob, Rian J. Dickstein, Shane Pearce, James M. Burke, Gary D. Steinberg; Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Mayo Clinic Rochester, Rochester, MN; University of California, San Diego Health, La Jolla, CA; Division of Urology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; BCG Oncology, Phoenix, AZ; Fox Chase Cancer Center, Philadelphia, PA; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; UCI Health, Orange, CA; SUNY Upstate Medical University, Syracuse, NY; Chesapeake Urology, Hanover, MD; Spokane Urology, Spokane, WA; Billings Clinic, Billings, MT; Rush University, Chicago, IL

Background: Cretostimogene grenadenorepvec is a type-5 oncolytic adenovirus designed to selectively replicate in bladder cancer cells with alterations in the retinoblastoma pathway. Additionally, the virus is engineered to express the GM-CSF transgene, resulting in a potent oncolytic immunotherapy mode of action. Cretostimogene monotherapy recently received Food and Drug Administration (FDA) Fast Track and Breakthrough Therapy Designations (BTD) in the BCG-Unresponsive, High-Risk, non-Muscle Invasive Bladder Cancer with Carcinoma in Situ (BCG-UR HR NMIBC with CIS) indication with a Complete Response (CR) at any time rate of 76%. This phase-2 study assessed the potential synergy between intravesical cretostimogene and pembrolizumab in patients with BCG-UR, HR NMIBC, with CIS, with or without Ta/T1 tumors. This combination has also received BTD from the FDA. **Methods:** 35 pts were treated with cretostimogene ($1x10^{12}$ viral particles) in combination with pembrolizumab at a dose of 400 mg IV q6 weeks. Cretostimogene induction was given as 6 weekly intravesical instillations followed by 3 weekly maintenance doses at months 3, 6, 9, 12, and 18. Pts with persistent CIS or high-grade Ta tumors at the 3mo assessment were eligible for re-induction. Pembrolizumab was administered for up to 24mo. Response assessments included cystoscopy, urine cytology, cross-sectional imaging, and mandatory bladder mapping biopsies at 12mo. The primary endpoint was CR at 12mo. Secondary endpoints included CR at any time, duration of response (DOR), CR at 24mo, cystectomy-free survival, and safety. Exploratory endpoints included analyses of baseline viral receptor expression, free E2F levels, PD-L1 status, urinary cytokine panels and measures of viral replication. **Results:** 30/35 pts are evaluable per protocol for the primary endpoint. Five pts discontinued prior to the 12mo time point. The CR rate in the Intention to Treat (ITT) population at 12mo and any time, was 57% (20/35) (95% CI 40-73%) and 83% (29/35) (95% CI 66-93%), respectively. Median DOR has not been reached but exceeds 21mo. The current CR rate in the ITT population at 24mo is 46% (16/35) (95% CI 29-63%). Three pts have yet to reach the 24mo time point. Cystectomy-free survival at 21mo is 80%. Complete data on the ITT and evaluable patient cohorts will be presented. Analyses of treatment-related adverse events (AE) are consistent with the individual agents and demonstrate no synergistic toxicity. **Conclusions:** The efficacy and safety of cretostimogene plus pembrolizumab for treatment of BCG-UR, HR NMIBC with CIS demonstrates best-in-class CR and DOR compared to current FDA-approved therapies, with an acceptable AE profile. Further investigation of this promising combination therapy is warranted and may serve to address a considerable unmet need. Clinical trial information: NCT04387461. Research Sponsor: CG Oncology.

Single agent axitinib in the management of patients with progressive pheochromocytoma and paraganglioma.

Antonio Tito Fojo, Andrea B Apolo, Maureen Edgerly, Karel Pacak, William Douglas Figg, Susan Elaine Bates, Jaydira Del Rivero; Columbia University College of Physicians and Surgeons, James J. Peters VAMC, New York, Bronx, NY; Genitourinary Malignancies Branch, CCR, NCI, NIH, Bethesda, MD; National Institutes of Health, Bethesda, MD; National Institutes of Child Health and Human Development, National Institutes of Health, Bethesda, MD; Clinical Pharmacology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD; Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Malignant pheochromocytomas and paragangliomas remain diseases that present those caring for patients with these diseases the dual challenges of hormonal excess and malignant behavior. Radiolabeled therapy with meta-iodobenzguanine (MIBG) and chemotherapy with a combination of cyclophosphamide, vincristine and dacarbazine can help in the management of patients whose disease has metastasized, but additional options are needed. The phase II FIRSTMAPPP study provided support for use of the tyrosine kinase inhibitor, sunitinib, in these malignancies with median PFS values of 8.9 vs. 3.6 months and ORRs of 31% vs. 8% for sunitinib vs placebo.Median duration of sunitinib therapy was 11 months. Concurrent with this study we launched a single arm trial to examine the activity of a similar TKI, axitinib. We report here the results of that study. **Methods:** Axitinib was self-administered at a dose of 5 mg every 12 hours continuously in a 28-day cycle. All patients were evaluated for dose adjustments to levels of 2, 3, 7, and 10 mg bid as options with intervals of at least 4 weeks between any dose escalations. Efficacy evaluations using conventional imaging were performed every 12 weeks. Documented evidence of disease progression was required prior to study entry. **Results:** Nineteen patients were enrolled; two did not receive treatment or less than one week of treatment. A partial response was achieved in 35.3% of patients, with a median reduction of tumor measurements of 34% and a median duration of response of 7.4 months. Median PFS was 7.9 months. Median duration of treatment was 9.5 months. Median OS was 29 months. Axitinib was well-tolerated with treatment-emergent adverse events with an attribution of possible, probable, and definite similar to those previously reported for the agent, including G1/2 fatigue, diarrhea, mucositis, and PPE in 42% to 63% and G1/2/3 hypertension in 79%, all managed with adjustments in antihypertensive medications No patient discontinued axitinib for an adverse event, nor had a prolonged suspension of treatment. Unfortunately, the study has been prematurely terminated by the sponsor. **Conclusions:** These results together with similar results reported recently with sunitinib provide strong evidence for the efficacy of sunitinib and axitinib, two VEGF tyrosine kinase inhibitors with similar characteristics, in the management of malignant pheochromocytoma and paragangliomas. Axitinib should be started at a dose of 5 mg bid and adjusted as tolerated. Despite its use in individuals with often difficult to treat hypertension, blood pressure management did not present a difficult challenge. Clinical trial information: NCT03839498. Research Sponsor: None.

Differentiating between adrenocortical carcinoma and pheochromocytoma by radiomics features at CT: A multi-institutional retrospective study.

Jingtong Zhang, Yinyao Chao, Kai Yao, Shengjie Guo; Department of Urology, State Key Laboratory of Oncology in Southern China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Zhongshan School of Medicine, Guangzhou, China; Department of Urology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Adrenocortical carcinoma (ACC), a highly malignant and rare tumor of the adrenal gland, shares similar CT characteristics with the less malignant pheochromocytoma (PHEO), resulting in low CT diagnostic accuracy. The standard therapeutic strategy for ACC differs from that of PHEO, making accurate diagnosis of ACC challenging but important. Radiomics offers an opportunity to classify adrenal tumors. However, previous research has primarily focused on differentiating malignant adrenal lesions from benign cases. In addition, the rarity of ACC makes it difficult to initiate large-scale studies, thus hindering further applications of radiomics. This study aimed to differentiate between ACC and PHEO using radiomics features based on contrast-enhanced CT. **Methods:** A total of 158 patients (median age, 47 years; inter-quartile range, 32-57 years; 76 males) pathologically diagnosed with ACC or PHEO between 2011 and 2023 were enrolled from three independent institutions. Radiomics features were extracted from different phases of contrast-enhanced CT images, and then selected by a two-step procedure. The radiomics model was developded and trained in the development cohort of 109 patients from Institution 1, then the model performance was tested in the test cohort of 49 patients from Institution 2 and 3. The area under the receiver operating characteristic curve (AUC) of the radiomics model was compared with two radiologists using the DeLong test. The SHAP method was used to improve the interpretability of the radiomics model. **Results:** We developed and tested a radiomics model that consisting of 10 selected radiomics features. In the test cohort, the radiomics model exhibited a significant improvement in diagnostic performance over 2 radiologists (AUC 0.92 vs. 0.79, 0.63) and achieved high accuracy (86%), sensitivity (81%) and specificity (88%) in differentiating between ACC and PHEO. Furthermore, the diagnostic process of this radiomics model was visualized using the SHAP method. **Conclusions:** To our knowledge, this is the first multi-institutional study to develop an interpretable radiomics model for preoperative differentiation between ACC and PHEO based on contrast-enhanced CT. The diagnostic performance of the radiomics model surpassed that of experienced radiologists, which may aid clinical decision making and improve treatment outcomes for ACC. Research Sponsor: China Postdoctoral Science Foundation, Grant No. 2023M744072.

Comparing treatment modalities for T2N0M0 muscle invasive bladder cancer: A propensity score analysis with the National Cancer Database.

Alberto Pieretti, Mohamed Mohanna, Saad Sabbagh, Nicolas Muruve, Hong Liang, Christopher Fleming, Christopher Weight, Nima Almassi, Georges-Pascal Haber, Ashish M. Kamat, Rafael Arteta-Bulos, Colin P.N. Dinney; Cleveland Clinic Florida, Weston Hospital, Weston, FL; Maroone Cancer Center, Cleveland Clinic Florida, Weston, FL; Cleveland Clinic Florida, Research Department, Weston, FL; Cleveland Clinic Florida, Department of Radiation Oncology, Cleveland, OH; Cleveland Clinic Glickman Urology and Kidney Institute, Cleveland, OH; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Muscle-invasive Bladder Cancer (MIBC) constitutes 25% of bladder malignancies. Per NCCN guidelines, the primary treatment for stage II (T2N0M0) MIBC is neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC), RC alone, or bladder preservation chemoradiotherapy (BPCRT). This study aims to compare the overall survival between different treatment modalities with an emphasis on patients considered to be best candidates for BPCRT (No hydronephrosis, extensive or multifocal carcinoma in situ (CIS), and tumor size <6cm, "low-risk") versus those who are not ("high-risk"). **Methods:** We queried 12510 patients from the National Cancer Database from 2004-2020 for stage II T2N0M0 MIBC. Patients were divided in low-risk (< 6 cm and no evidence of CIS) or high-risk MIBC. The propensity score matched (PSM) sample was constructed greedy nearest neighbor matching on the logit of the propensity score using a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score. We used standardized differences (SD) to evaluate how well the covariates were balanced and a value of < 0.1 was considered negligible. The Cox proportional hazards model was performed to compare the survivorships between the PSM paired samples. All data analyses were conducted using SAS version 9.4. **Results:** Following PSM and risk factor stratification, we found that median overall survival (OS) was lower with BPRCT compared to RC alone or NAC+RC in both risk groups. In the low-risk group, the median OS of BPRCT compared to NAC+RC was 34 and 76 months, respectively (HR = 1.81, 95%CI = (1.25-2.62), p=0.0017 and there was no statistical significant difference in RC compared to NAC+RC median OS (p=0.3459). In the high-risk group, the median OS of BPRCT compared to NAC+RC was 22 and 68 months, respectively (HR = 2.19, 95%CI = (1.86-2.59), p<0.0001) (Table) and the median OS of RC compared to NAC+RC was 79 and 99 months respectively (HR=1.2, 95%CI = (1.11-1.3), p<0.001 (Table). **Conclusions:** This nationwide study showed that RC was the optimal treatment for low-risk stage 2 MIBC, with improved OS compared with BPCRT and equivalent OR with NAC+RC, without the added cost or morbidity. For high-risk patients NAC+RC was associated with a significant improvement of OS compared to BPCRT and RC alone. Research Sponsor: None.

Survival comparison of different treatment modalities.

	HR	95%CI	p-value
(1) RC vs. NAC+RC for whole patients	1.23	(1.15-1.31)	<0.0001
(1.1) RC vs. NAC+RC for patients with tumor size > 6 cm and/or CIS	1.20	(1.11-1.30)	<0.0001
(1.2) RC vs. NAC+RC for patients with tumor size ≤ 6 cm and no-CIS	1.10	(0.90-1.33)	0.3459
(2) BPCRT vs. NAC+RC for whole patients	1.95	(1.70-2.25)	<0.0001
(2.1) BPCRT vs. NAC+RC for patients with tumor size > 6 cm and/or CIS	2.19	(1.86-2.59)	<0.0001
(2.2) BPCRT vs. NAC+RC for patients with tumor size ≤ 6 cm and no-CIS	1.81	(1.25-2.62)	0.0017

Prognostic factors of relapse in surgically resected small cell neuroendocrine carcinomas of the urothelial tract (SCNEC-URO).

Mohammad Jad Moussa, Nathaniel R. Wilson, Lianchun Xiao, Georges C. Tabet, Jianjun Gao, Amishi Yogesh Shah, Paul Gettys Corn, Sangeeta Goswami, Pavlos Msaouel, Nizar M. Tannir, Byron H. Lee, Ashish M. Kamat, Mehrad Adibi, Colin P.N. Dinney, Donna E. Hansel, Charles C. Guo, Arlene O. Siefker-Radtke, Matthew T Campbell, Omar Alhalabi; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Hematology and Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, Division of Pathology and Laboratory Medicine, Houston, TX; Department of Urology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: SCNEC-URO are rare aggressive cancers with limited treatments. Although they frequently co-exist (60-70%) with urothelial carcinoma (UC) at diagnosis, most metastatic biopsies of relapsing patients (pts) show pure small cell (SC) morphology. There are major unmet needs to predict relapse after definitive surgery. **Methods:** Data was extracted from a historical cohort of n=216 pts with surgery for surgically resectable disease (cT1-T4, N0 or N+, M0) at MD Anderson between November 1985 and June 2021. Morphology at resection was defined as: 'pCR' (pathological complete response, including no residual carcinoma or carcinoma in situ), 'Any SCNEC' (persistence of SC with UC in sample) or 'Non-SCNEC' (UC only). Relapse events after surgery were analyzed as time-to-event (TTE) outcome with competing risk non-parametric method. Univariable and multivariable analyses identified prognostic factors of relapse. **Results:** In TTE analysis, cohort events (n=216) included: n=70 censored (alive and relapse-free), n=92 failure events (with relapse), and n=54 competing events (death without known relapse). n=154 (71.3%) received neoadjuvant chemotherapy, including SCNEC regimens in 125/154 (81.2%) and UC regimens in 16/154 (10.4%). The 5-year cumulative incidence function (CIF) of relapse for all pts was 41.92% [95% CI: 35.2% - 48.5%]. CIF rates were significantly different per morphology at resection (Gray's test, $p<.0001$). Pts with pCR had the lowest 5-year CIF rate for relapse (18.5%) [11.1% - 27.4%], while pts with 'Any SCNEC' had the highest CIF (69.6%) [58.6% - 78.9%]. Pts with Non-SCNEC had an intermediate CIF risk (31.6%) [17.6% - 46.7%]. Staging at resection also showed different CIF rates (Gray's test, $p<.0001$). Pts with pT0N0 had the lowest CIF rate (12.8%) [5.6% - 23.2%], with CIF rates increasing with higher staging: pTisN0 (25%) [11.6% - 41%]; pT1N0 (25%) [5.4% - 51.7%]; pT2 or greater, but N0 (52.4%) [41% - 62.7%]. Pts staged node-positive (pN+) did not have an estimated 5-year CIF as most died within 5 years. In multivariable analysis, clinical staging at diagnosis, pathological staging and cellular morphology at resection were associated with relapse (Table). **Conclusions:** Besides staging at diagnosis and surgery, morphology at resection is a key predictor of relapse. Persistence of the SC component predicts a higher chance of relapse than its eradication and persistence of the UC component. While adjuvant therapy in UC has made significant progress recently, a tailored adjuvant approach addressing the residual SC component at definitive surgery is needed to improve outcomes and decrease relapse. Research Sponsor: None.

Parameter		HR	95% CI		*p*-value
Stage at Diagnosis	T3/4, N0/N+ vs. T1-T2N0	1.642	1.067	2.527	**0.0241**
Stage at Surgical Resection	N0 vs. N+	0.429	0.259	0.71	**0.001**
Morphology at Resection	Any SCNEC vs. Non-SCNEC	2.81	1.476	5.351	**0.0017**
	pCR vs. Non-SCNEC	0.703	0.339	1.457	0.343

Survival outcomes of small cell variant bladder cancer: Analysis from nationwide study.

Mohammad Arfat Ganiyani, Atulya Aman Khosla, Shahzaib Ahmad, Karan Jatwani, Shreyas S Bellur, Nouman Aziz, Muni Rubens, Mukesh Roy, Bruno R. Bastos, Manuel Ozambela Jr., Ahmed Eldefrawy, Murugesan Manoharan, Rohan Garje; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Corewell Health William Beaumont University Hospital, Royal Oak, MI; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Wyckoff Heights Medical Center, Brooklyn, NY

Background: Small cell carcinoma of bladder (SCB) is a rare and aggressive histological subtype. While the survival impact of various treatment modalities for the classic urothelial bladder cancer has been well-researched, limited studies exists on the survival outcomes of these treatment modalities in patients with SCB, primarily due to the exclusion of these patients from clinical trials. This study aims to explore the impact of different treatment modalities on the survival outcome of patients with SCB using data from a large nationwide registry. **Methods:** This retrospective study queried the National Cancer Database from 2004 to 2020 and followed STROBE guidelines. The primary analytic cohort included patients diagnosed with locoregional SCB based on the TNM stage (T1-T4, N0-N3, M0). Treatment modalities comprised perioperative systemic therapy combined with definitive surgery (PST), concurrent chemoradiation (CR), surgery only (S), Radiation therapy only (RT) and systemic therapy only (ST). This study utilized Kaplan-Meier survival analysis and the Cox Proportional regression. **Results:** The study included 4,658 patients with locoregional SCB. The analysis revealed 236 (4.82%) patients with SCB received PST, 752 (15.36%) got CR, 612 (12.50%) underwent S, 3,029 (61.85%) received ST, and 268 (5.47%) had RT. The median overall survival was 64.49 months (CI: 41.4-75.1, $P < 0.001$) with PST, 29.27 months (CI: 22.9-35.88), with CR, 14.13 months (CI: 9.92-21.65) with S alone, 21.29 months (CI: 18.53-23.69) with ST, and 7.82 months (CI: 6.24-9.53) with RT alone. In the multivariate analysis, combining perioperative systemic therapy with surgery led to a 54% reduction in hazards of death (HR: 0.46; CI: 0.37-0.58) compared to surgery alone, whereas CCR achieved a 41.16% (HR: 0.59; CI: 0.47-0.73) decrease in hazard, illustrating the effectiveness of multimodal treatment for SCB. **Conclusions:** Treatment approaches with either systemic therapy combined with definitive surgery or concurrent chemoradiation enhanced survival outcomes, highlighting the significance of a multimodal approach for patients with SCB. Research Sponsor: None.

Cox proportional hazard analysis in patients with SCB.

Variable	Hazard Ratio	P-value	95 % CI
Surgery Only	ref		
Concurrent chemoradiation	0.58	**<0.0001**	0.47 - 0.73
Perioperative Systemic Therapy	0.46	**<0.0001**	0.36 - 0.58
Systemic therapy only	0.68	<0.0001	0.55 - 0.83
RT only	1.59	<0.0001	1.24 - 2.05
CDCC = 0, 1	ref		
CDCC = 2 and >= 3	1.28	<**0.0001**	1.11 - 1.47
Node Negative	ref		
Node Positive	1.36	**0.001**	1.13 - 1.64

TPS4607 Poster Session

FIT-001: A phase 1 clinical trial of the farnesyl transferase inhibitor KO-2806 alone or as part of combination therapy for advanced solid tumors.

Glenn J. Hanna, Douglas Adkins, Jacob Stephen Thomas, Justine Yang Bruce, Manish R. Patel, Guru P. Sonpavde, Jason Timothy Henry, Nawal Bendris, Zijing Zhang, Amitava Mitra, Amaya Gasco Hernandez, Andrew Saunders, Stephen Dale; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Department of Medicine, Division of Oncology, Washington University School of Medicine, St Louis, MO; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; Carbone Cancer Center, University of Wisconsin, Madison, WI; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; AdventHealth Cancer Institute, Orlando, FL; Sarah Cannon Research Institute at HealthONE, Denver, CO; Kura Oncology, Inc., Boston, MA

Background: Farnesyl transferase inhibitors (FTIs) block post-translational modification of RAS and other farnesylated proteins. HRAS-driven tumors are highly sensitive to FTI treatment. Recent clinical trials (NCT03719690, NCT02383927) of the FTI, tipifarnib, in patients with *HRAS*-mutant (*HRAS*-m) head and neck squamous cell carcinoma harboring high variant allele frequency mutations (VAF ≥20%), showed objective response rates of up to 50% and favorable long-term outcomes. KO-2806 is a next-generation FTI that has increased potency and improved pharmacokinetic properties. In preclinical studies, KO-2806 has been shown to: (1) enhance tumor growth inhibition of tyrosine kinase inhibitors, including cabozantinib, in multiple clear cell renal cell carcinoma (ccRCC) cell line- and patient-derived xenograft models; and (2) enhance activity of KRAS inhibitors, including adagrasib, in *KRAS* mutant non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and pancreatic ductal adenocarcinoma (PDAC) mouse models. These preclinical data support clinical investigation of KO-2806 alone and in combination therapy. **Methods:** FIT-001 is a first-in-human, multicenter, open-label clinical trial that will evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics (Pd), and preliminary antitumor activity of KO-2806 as monotherapy or in combination therapy in advanced solid tumors (KO-2806-001; NCT06026410). Up to 270 patients will be enrolled in phase 1a and phase 1b combined across 50 sites. Phase 1a will have separate monotherapy and combination dose-escalation arms. As monotherapy, the study will enroll patients with *N/K/HRAS* alterations in specific solid tumor types, such as NSCLC, CRC, and PDAC, who are refractory to standard-of-care therapies. KO-2806 and cabozantinib will be combined in patients with advanced or metastatic ccRCC who progressed on ≥1 prior line of immunotherapy-based systemic therapy; KO-2806 and adagrasib will be combined in patients with *KRAS-G12C* mutant locally advanced or metastatic NSCLC who received ≥1 prior systemic therapy. On the basis of emerging data from phase 1a, two Pd cohorts (n≤12) with mandatory pre- and on-treatment tumor biopsies may be enrolled. In each Phase 1b dose expansion, patients will receive the recommended phase 2 dose [RP2D] of KO-2806 with cabozantinib (in ccRCC) or adagrasib (in NSCLC), or will be randomized by dose if 2 potential KO-2806 RP2Ds are identified for a combination. Other combination arms may also be considered. The study began accrual in October 2023. Clinical trial information: NCT06026410. Research Sponsor: Kura Oncology, Inc.

TPS4608 Poster Session

PRadR: PSMA targeted radionuclide therapy in adult patients with metastatic clear cell renal cancer, a multicentric phase I/II.

Armelle Vinceneux, Anne-Sophie Bidaux, Claire Cropet, Delphine Tatu, Mathilde Bernardin, Séverine Neymarc, David Pérol, Jean-Pierre Pouget, Julie Constanzo, Nicolas Foray, Loic Djaileb, Antony Kelly, David Kryza, Anne-Laure Giraudet; Department of Medical Oncology, Centre Léon Bérard, Lyon, France; Department of Clinical Research, Centre Léon Bérard, Lyon, France; Department of Biostatistics, Centre Léon Bérard, Lyon, France; Institut de Recherche en Cancérologie de Montpellier, Montpellier Cedex 5, France; Institut de Recherche en Cancérologie de Montpellier, Montpellier, France; Inserm U1296, Radiations Defense, Health and Environment, Lyon, France; Department of Nuclear Medicine, Grenoble Alpes University Hospital, Grenoble, France; Nuclear Medicine Department, Centre Jean Perrin, Clermont-Ferrand, France; UNIV Lyon-Université Claude Bernard Lyon 1, LAGEPP UMR 5007 CNRS, Villeurbanne, France; Lumen Nuclear Medicine Department, Centre Léon Bérard, Lyon, France

Background: Prostate Specific Membrane Antigen (PSMA) is highly expressed in neovessels of various solid tumors including Renal Cell Carcinoma, especially clear cell (ccRCC), which is the most frequent sub type. In ccRCC, PSMA expression in tumor vessels is correlated with higher grade and stage as well as in match between primary tumor and metastasis. PSMA may be a target expressed in metastatic ccRCC for radionuclide therapy using PSMA Ligands Radiolabeled with Lutetium-177 (PRLT), which is already used in daily practice for prostate cancer. ^{177}Lu-PSMA in prostate cancer with renal impairment appeared to be feasible and tolerable in previous studies. The aim of this Phase I/II study NCT06059014 is to assess the safety and clinical activity of this new Radiolabelled Therapy for mccRCC. **Methods:** PRadR is a multicentric, single-arm, open-label Phase I/II study evaluating PSMA targeted radionuclide therapy in adult patients with mccRCC. Patients must have received at least 2 prior regimens, including immunotherapy and antiangiogenic agents as per international guidelines, ECOG 0 to 1, with adequate hematologic, hepatic and renal function with a creatinine clearance according to CKD-EPI $\geq$ 40 mL/min/1.73m^2. Only patients with tumor tracer uptake greater than background will be treated with 4 cycles of 7.4 GBq of ^{177}Lu-PSMA-1 every 6 weeks. The primary endpoints are the incidence of severe toxicity (Safety run in) and the disease control rate at 24 weeks (DCR-24W) as per RECIST V1.1 (Phase II) in patients with a PSMA-positive mccRCC selected through ^{68}Ga-PSMA PET. Secondary endpoints include overall response rate, duration of response, progression free survival, overall survival and safety according to NCI-CTCAE V5.0. During the safety run in, if more than one patient experiences severe toxicity during the first cycle over the first 6 treated patients, then a lower activity of ^{177}Lu-PSMA-1 will be evaluated in an additional cohort of 6 patients (5.9 GBq). Using a Fleming-A'Hern single stage design with a target DCR_{24w} of 30% and an inefficacy bound of 10% (α=5% one sided and 90% power) a total of 33 evaluable patients are required. If at least 7 successes (CR, PR or SD) at 24 weeks of treatment are observed, ^{177}Lu-PSMA-1 will deserve further investigation in this setting. Translational studies will consist in comparing efficacy and toxicity to dosimetry of 177Lu-PSMA-1 in normal tissues and tumor lesions, and biomarkers obtained from blood samples or tumor tissues. First patient was enrolled in November 2023. Clinical trial information: NCT06059014. Research Sponsor: None.

TPS4609 Poster Session

Phase 2 trial for sequential treatment of high dose cabozantinib (CABO) or CABO plus nivolumab (NIVO) on/after progression on CABO monotherapy in advanced renal cell carcinoma (RCC): Seq-Cabo.

Qian Qin, James Brugarolas, Hans J. Hammers, Waddah Arafat, Kevin Dale Courtney, Jue Wang, Changchuan Jiang, Song Zhang, Charles Lance Cowey, Thomas E. Hutson, Tian Zhang; Division of Hematology and Oncology, Department of Internal Medicine, University of Texas Southwestern, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; Peter O'Donnell Jr. School of Public Health, University of Texas Southwestern, Dallas, TX; Baylor University Medical Center/Texas Oncology, Dallas, TX; Baylor University Medical Center, Texas Oncology, Dallas, TX

Background: Efficacy outcomes for advanced RCC have improved with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (IO), and CABO has become an established treatment for both front-line and refractory, advanced RCC. However, most patients develop resistance to CABO. With each subsequent line of therapy, efficacy and survival benefits also shorten and treatment options become limited. It is thus important to explore ways to maximize each line of therapy. **Methods:** Based on previous studies suggesting 1) dose-dependent effect of VEGFR-TKIs with feasibility/efficacy of CABO dose escalation to 80mg and 2) immune-modulatory effects of CABO, we have designed a two-cohort phase 2 trial to salvage CABO response, either by escalating the dose of CABO to 80mg oral (PO) daily (cohort 1) or by combining CABO 40mg PO daily with NIVO 480mg intravenous (IV) every 4 weeks (cohort 2), based on investigator choice. Subjects will be treated until progression or unacceptable toxicity. Main inclusion criteria include progressive advanced RCC after prior CABO monotherapy for at least 6 months, able to tolerate CABO 60mg PO daily (cohort 1) and 40mg PO daily (cohort 2), radiographically measurable disease, ECOG < 2, and adequate end-organ function. Main exclusion criteria include prior treatment with concurrent CABO/NIVO, uncontrolled co-morbidities, uncontrolled HIV, and concurrent malignancy (excepting completely excised skin cancers and organ-confined Gleason 6 prostate cancer). Primary endpoint is progression free survival (PFS) with key secondary endpoints including overall response rate, disease control rate, duration of response, and overall survival. The null hypothesis of median PFS 3 months will be tested against an alternative hypothesis of median PFS 6 months. Assuming a 2-sided significance level of 10% and 80% power, and estimating 10% drop out, 18 patients per cohort (36 patients total) will be enrolled.Pharmacokinetics, circulating biomarkers, and pre-/post-biopsies are planned for tissue-based analyses. The study is open for enrollment (NCT05931393). Clinical trial information: NCT05931393. Research Sponsor: Exelixis.

TPS4610 Poster Session

Phase 1b/2 study of combination ^{177}Lu girentuximab plus cabozantinib and nivolumab in treatment naive patients with advanced clear cell RCC.

Eric Jonasch, Elshad Hasanov, Lesley Flynt, Hyunsoo Hwang, Rebecca Slack Tidwell, Roserika Brooks, Lauren Michelle Wood, Travis Solley, Dahlia Mack, Yuko Yamamura, Aradhana M. Venkatesan; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Complete response (CR) is still a rare event in patients with advanced clear cell renal cell carcinoma (ccRCC). The combination of nivolumab plus cabozantinib was recently approved for the first-line treatment of ccRCC based on the CheckMate 9ER phase 3 study demonstrating improved progression-free survival (PFS) and objective response rate (ORR) in comparison to sunitinib. However, the CR rate was only 9%. Since the anti-tumor effects of immune checkpoint inhibitors are dependent on the presence of activated tumor-infiltrating T cells, drugs that could synergize with T cells' anti-tumor activity can allow us to improve CR rates. Activation of the cGAS-STING pathway which is induced by radiation-induced DNA damage, is one promising mechanism that has been investigated. Many studies have shown that radiation treatment augments immune checkpoint inhibition. However, it is not always possible to radiate all metastatic lesions. Therefore, targeted peptide receptor radionuclide therapies, have been developed by conjugating radioisotopes to receptor binding analogs targeting specific cancer cell surface proteins, thereby delivering targeted radiation to cancer cells in the body with minimal damage to surrounding healthy cells. ^{177}Lu girentuximab is the first antibody-radioisotope designed for ccRCC, targeting carbonic anhydrase 9-expressing cells, which includes >90% of ccRCC. It has been tested in metastatic ccRCC as a single agent and shown to be safe and effective in stabilizing disease in 57% of pts. In this study, we hypothesize that ^{177}Lu girentuximab-induced DNA damage will potentiate the STING pathway, and this activation will synergize with nivolumab and cabozantinib to promote trafficking and infiltration of activated T cells to tumors and achieve higher CR rates. **Methods:** Up to 100 patients with treatment naive, biopsy-proven ccRCC with adequate organ/marrow function with 1 evaluable lesion by RECIST 1.1 will be enrolled. A 5-patient safety lead-in will evaluate myelosuppression. Ongoing safety, and futility monitoring will employ a Bayesian approach. The sample size was chosen for reasonable operating characteristics to distinguish a CR rate (primary endpoint) of 18% as better than 9% using a beta(0.09, 0.91) prior. Secondary endpoints are ORR, PFS by RECIST 1.1, and overall survival. ^{177}Lu-girentuximab 1480 MBq/m^2 (61% of single agent MTD) will be administered every 12 weeks for up to 3 cycles. Starting with the second cycle, nivolumab and cabozantinib will be added at standard dose. To explore the effects of the treatment on inducing activated T cell infiltration, patients will undergo pre/post-treatment PET scan with ^{18}F-AraG radiotracer as well as biopsies for single cell, spatial transcriptomics and proteomics studies. Clinical trial information: NCT05663710. Research Sponsor: DOD grant W81XWH-22-1-0456.

TPS4611 Poster Session

Zanzalintinib (XL092) plus nivolumab in non-clear cell renal cell carcinoma: The randomized phase 3 STELLAR-304 study.

Sumanta Kumar Pal, Thomas Powles, Ravindran Kanesvaran, Mohan Liu, Zhong Wang, Aarohi Bhatt, Pritesh Patel, Cristina Suárez; City of Hope Comprehensive Cancer Center, Duarte, CA; Barts Health NHS Trust Saint Bartholomew's Hospital, London, United Kingdom; National Cancer Centre, Singapore, Singapore; Bristol Myers Squibb, New York, NY; Exelixis, Inc., Alameda, CA; Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

Background: Non-clear cell renal cell carcinoma (nccRCC) is a heterogenous group of rare, histologic subtypes with limited treatment options. There have been few dedicated randomized controlled studies in nccRCC, and novel treatment options supported by data from robust clinical trials are needed. Sunitinib, a tyrosine kinase inhibitor (TKI), is a commonly used therapy for nccRCC based on clinical benefit demonstrated in phase 2 trials. To date, no treatment has shown a significant overall survival (OS) improvement over sunitinib in any nccRCC subtype. Monotherapy with immune checkpoint inhibitors (ICIs) has shown only modest response rates, but TKI-ICI combinations have shown promising clinical activity in single-arm phase 2 trials. Zanzalintinib is a novel, multi-targeted TKI of VEGFR, MET, and the TAM kinases (TYRO3, AXL, MER) which are involved in tumor angiogenesis, metastasis, and immunosuppression. Zanzalintinib has shown antitumor and immunomodulatory activity in animal models when used alone or in combination with ICIs (Hsu et al. *Mol Cancer Ther.* 2023). In the phase 1 STELLAR-001 study, single-agent zanzalintinib showed promising antitumor activity (38% objective response rate [ORR] and 88% disease control rate) and a manageable safety profile in patients with heavily pretreated advanced clear-cell RCC (Pal et al. IKCS NA 2023. Abs 1). STELLAR-304 was designed to assess the efficacy and safety of zanzalintinib + nivolumab versus sunitinib in previously untreated advanced nccRCC. **Methods:** STELLAR-304 (NCT05678673) is a phase 3, global, randomized, open-label study enrolling patients ≥18 years of age with unresectable/advanced/metastatic nccRCC. Patients must have measurable disease per RECIST v1.1, a Karnofsky performance status of ≥70%, and papillary, unclassified, or translocation-associated histology (sarcomatoid features are allowed). Patients with chromophobe, renal medullary carcinoma, or pure collecting duct histology are excluded. Prior systemic anticancer therapy for advanced/metastatic nccRCC is not allowed; however, one prior systemic adjuvant therapy, including ICI (but excluding sunitinib), is permitted for completely resected RCC if recurrence occurred ≥6 months after the last adjuvant therapy dose. Patients (N=291) are randomized 2:1 to receive treatment with zanzalintinib + nivolumab, or sunitinib alone. The dual primary endpoints are progression-free survival and ORR per RECIST v1.1 by blinded independent radiology committee. The secondary endpoint is OS; safety will also be assessed. STELLAR-304 is currently recruiting patients in Europe, North and South America, and the Asia-Pacific region. Clinical trial information: NCT05678673. Research Sponsor: Exelixis, Inc.

TPS4612 Poster Session

Phase 2 study of combination tivozanib and nivolumab in advanced non-clear cell renal cell carcinoma (RCC): FORTUNE trial.

Charles B. Nguyen, Ulka N. Vaishampayan, Matthew T Campbell, Hans J. Hammers, Roserika Brooks, Travis Solley, Lauren Michelle Wood, Eric Jonasch, Ajjai Shivaram Alva; Rogel Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI; Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Non-clear cell RCC (nccRCC) accounts for 25% of RCC cases and encompasses a heterogeneous group of tumors with poor prognosis. Most RCC trials have enrolled clear cell RCC (ccRCC) and excluded nccRCC. Due to the rarity of nccRCC and limited prospective data, there is a need to develop effective therapies for nccRCC. Tivozanib is a selective VEGFR1-3 tyrosine kinase inhibitor (TKI) approved for patients (pts) with metastatic ccRCC who have had at least 2 prior lines of therapy, one of which included a VEGFR TKI. In nccRCC, tivozanib had an unconfirmed objective response rate (ORR) of 32% and disease control rate of 74% in a subgroup analysis of a phase 2 study. The combination of tivozanib and nivolumab has been evaluated in a phase 1b/2 study which showed an ORR of 56% in metastatic ccRCC, and results from the subsequent phase 3 trial are awaited. However, this combination has not been studied in nccRCC. Based on the potential activity of tivozanib in nccRCC and promising results of the combination with nivolumab, we hypothesize that tivozanib and nivolumab may be efficacious in advanced nccRCC. **Methods:** FORTUNE is a multi-center, single arm, phase 2 trial assessing the efficacy of tivozanib and nivolumab in pts with advanced nccRCC. Pts with histologically-confirmed metastatic nccRCC of any nccRCC histology (except medullary and collecting duct tumors) who are either treatment-naïve or have received up to 1 line of systemic therapy (including prior immunotherapy) with measurable disease per RECIST 1.1 will be eligible. Enrolled pts will receive oral tivozanib 0.89 mg daily on days 1-21 of 28-day cycles in combination with nivolumab 480 mg on day 1 every 28-day cycles. Treatment will continue until disease progression, death, intolerable toxicity, or consent withdrawal. The primary endpoint is ORR by RECIST 1.1. Key secondary endpoints include progression-free survival, overall survival, duration of therapy, and adverse events (AEs). The trial will utilize a Bayesian optimal phase 2 (BOP2) design with a planned accrual of 48 total pts in 12-patient cohorts with interval safety and toxicity analyses. After the first 12-patient cohort is enrolled, the study will stop if only 1 pt has a response or if >5 pts develop a treatment-limiting AE. Otherwise, the study will continue enrolling pts in 12-patient cohorts for a total of 48 pts with additional interval stopping boundaries for efficacy and safety. This trial will test the joint null hypothesis that the true ORR rate is 15% (vs 30%) and a null hypothesis that the treatment-limiting AE rate is 40% (vs 20%) against their one-sided alternative at a 0.025 type I error. Exploratory analyses with circulating tumor DNA (pre-treatment, cycle 2, and end of treatment), archival tissue, and on-treatment biopsy (cycle 4) are planned to examine the biologic correlates associated with therapy response. Enrollment began in January 2024. Clinical trial information: NCT06053658. Research Sponsor: AVEO Pharmaceuticals, Inc.

TPS4613 **Poster Session**

NRG-GU012: Randomized phase II stereotactic ablative radiation therapy (SABR) for metastatic unresected renal cell carcinoma (RCC) receiving immunotherapy (SAMURAI).

William A. Hall, Theodore Karrison, Bradley Alexander McGregor, Pedro C. Barata, Himanshu Nagar, Chad Tang, shankar siva, Todd Matthew Morgan, Joshua Michael Lang, Carri Glide-Hurst, Sophia C. Kamran, Karthik Sundaram, Sharyn I. Katz, Felix Y Feng, Rana R. McKay; Medical College of Wisconsin, Milwaukee, WI; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; University Hospitals Seidman Cancer Center, Cleveland, OH; Weill Cornell Medicine, New York, NY; Department of Genitourinary Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; University of Michigan, Ann Arbor, MI; University of Wisconsin Carbone Cancer Center, Madison, WI; Massachusetts General Hospital, Harvard Medical School, Boston, MA; University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; Radiology School of Medicine, University of California, San Francisco, San Francisco, CA; University of California, San Diego Health, La Jolla, CA

Background: The treatment landscape for patients with metastatic RCC has been evolving over the past decade. The current standard of care for patients presenting with de novo metastatic disease is combination immunotherapy (IO)-based treatment. At the time of this shift in the systemic treatment strategy for patients advanced disease, the role of immediate cytoreductive nephrectomy has also been in flux. For patients with de novo disease, there has been a shift towards initiation of upfront systemic rather than immediate cytoreductive nephrectomy. SABR is a highly focused radiation technique that delivers a high dose of radiation over a limited number of fractions. The SAMURAI trial seeks to evaluate SABR as an alternative approach to treat the primary tumor in patients with metastatic RCC receiving IO, who are not recommended for surgery, or who decline surgery. **Methods:** This is a randomized phase II trial for patients with metastatic RCC with an intact primary tumor. Eligible patients include those with any histology RCC who are candidates to receive standard IO combination treatment and are those not recommended for upfront surgery or decline surgery. Patient may have initiated IO-based treatment up to 90 days prior to enrollment. Patients will be randomized to SABR + IO combination versus IO combination alone. The primary objective of the study is to determine whether the addition of SABR to the primary tumor in combination with IO improves outcomes compared to IO alone in patients with metastatic, unresected, RCC. The primary endpoint is nephrectomy and radiographic progression-free survival (nrPFS) with progression determined as per iRECIST criteria. Patients are eligible if they are not recommended for upfront surgery, have a primary tumor treatable with SABR, and are candidates for IO. Choice of IO combination regimen will be at the discretion of the treating physician and will include either IO-IO or regimens of IO in combination with a VEGF inhibitor (IO-VEGF). 240 patients will be randomized in a 2:1 ratio favoring SABR plus IO combination (n=160) as compared to standard of care IO combination alone (n=80). The sample size will provide 90% power at a one-sided alpha level of 0.05 to detect a hazard ratio for nrPFS of 0.62, i.e., an approximate 40% reduction in the rate of events. Secondary endpoints include objective response rate by iRECIST and RECIST, radiographic progression free survival by RECIST and iRECIST, time to second line therapy, rate of cytoreductive nephrectomy, treatment free survival, and overall survival. Exploratory analyses will assess potential prognostic and predictive biomarkers. The trial is currently open and accruing through the NRG oncology cooperative group (NCT05327686) and study information can be found through the Cancer Trials Support Unit website www.ctsu.org.
Research Sponsor: This project was supported by grants U10CA180822 (NRG Oncology SDMC), U24CA196067 (NRG Specimen Bank), U10CA180868 (NRG Oncology Operations), U24CA180803 (IROC) from the National Cancer Institute (NCI).

TPS4614 Poster Session

Advanced renal cell cancer combination immunotherapy clinical trial (ARCITECT; HCRN GU 22-587).

Michael Thomas Serzan, Opeyemi Jegede, Robert S. Alter, Mehmet Asim Bilen, David A. Braun, David Johnson Einstein, Naomi B. Haas, Daniel Herchenhorn, Jennifer King, Karie Runcie, Jeffrey A. Sosman, Cora N. Sternberg, Yuanquan (Aaron) Yang, Sabina Signoretti, Toni K. CHOUEIRI, Michael B. Atkins; Dana-Farber Cancer Institute, Boston, MA; Regional Cancer Care Associates, Hackensack, NJ; Winship Cancer Institute of Emory University, Atlanta, GA; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Beth Israel Deaconess Medical Center, Boston, MA; University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; University of California, San Diego (UCSD), San Diego, CA; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Columbia University Irving Medical Center, New York, NY; Northwestern University, Chicago, IL; Hematology/Oncology, Weill Cornell Medicine, New York, NY; Pelotonia Institute for Immuno-Oncology and Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Brigham and Women's Hospital, Boston, MA; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC

Background: First-line treatment for patients with metastatic clear cell renal cell carcinoma (mccRCC) often includes an anti-PD1 inhibitor in combination with either an anti-CTLA inhibitor (IO/IO) or a VEGF receptor tyrosine kinase inhibitor (TKI) (IO/TKI). Although some patients treated with nivolumab/ipilimumab (Nivo/Ipi) (IO/IO) experience durable responses leading to treatment free intervals, over two-thirds experience disease progression. Resistance to Nivo (anti-PD1) monotherapy has been associated with increased presence of a subpopulation of Tregs in the tumor microenvironment. Botensilimab (Bot) is an IO agent that leverages novel FcyR-associated mechanisms of action to enhance T cell priming, deplete intratumoral Tregs and enhance myeloid activation. Combination botensilimab/balstilimab (Bot/Bal) (anti-CTLA/anti-PD1) has shown impressive anti-tumor activity in diseases where Nivo/Ipi has shown little to no efficacy. **Methods:** ARCITECT is a phase II, multicenter investigator initiated trial evaluating the efficacy and safety of Bot/Bal relative to Nivo/Ipi. Patients with mccRCC (favorable, intermediate, or poor risk), no prior systemic therapy (including adjuvant or neoadjuvant), and at least one measurable lesion as defined by RECIST 1.1 are eligible for enrollment. 120 patients will be randomized in a 2:1 fashion to Arm A (Bot/Bal induction followed by Bal maintenance) or Arm B (Nivo/Ipi induction followed by Nivo maintenance) each for a maximum of 2 years. Stratification factors include IMDC risk groups and sarcomatoid histology. The primary endpoint is overall response rate (ORR) per RECIST 1.1. We hypothesize that Bot/Bal will lead to a superior ORR (55%) relative to Nivo/Ipi (40%). This trial has $>$ 90% power to detect the alternative hypothesis while maintaining a one-sided significance level of not more than 0.10 using the exact binomial. The study will be monitored for early stopping in favor of the null hypothesis based on a Simon's two stage design. In the first stage, 69 patients will be enrolled (Arm A:46 and Arm B:23). If at the end of the first stage, Arm A has either at least 18/42 (42.8%) of eligible patients responding or an ORR at least numerically equivalent to that for eligible patients in Arm B, then the trial will progress to the second stage. The primary endpoint will be met if there are 38/80 responders (ORR $>$ 47.5%) in Arm A. Key secondary endpoints include landmark progression-free survival, treatment-free survival and rates of immune-related adverse events. Correlative studies will explore immune and molecular predictors of response and resistance to IO/IO in tumor and blood. Clinical trial information: NCT05928806. Research Sponsor: Agenus; HCRN.

TPS4615 **Poster Session**

Enfortumab vedotin plus pembrolizumab in the treatment of locally advanced or metastatic bladder cancer of variant histology: A phase II study.

Bassel Nazha, Jacqueline T Brown, Yuan Liu, Haydn Kissick, Bradley Curtis Carthon, Omer Kucuk, Lara R Harik, Vikram M Narayan, Shreyas S Joshi, Mehmet Asim Bilen; Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA; Department of Urology, Emory University School of Medicine, Atlanta, GA; Department of Pathology, Emory University School of Medicine, Atlanta, GA; Department of Urology, Emory University, Atlanta, GA; Winship Cancer Institute of Emory University, Atlanta, GA

Background: Bladder cancers of variant histology (BCVH) account for up to 25% of bladder cancer incidence and affected patients (pts) usually have poor outcomes. The treatment options are limited due to the underrepresentation or exclusion of BCVH pts from trials for locally advanced or metastatic urothelial cancer (mUC). Enfortumab vedotin (EV) is an antibody-drug conjugate specific for Nectin-4. In the EV 302 Phase III trial, EV+pembrolizumab (pembro) significantly prolonged overall survival (OS) compared to platinum-based chemotherapy in mUC (HR 0.47, 95% CI 0.38-0.58) and was recently FDA-approved as standard of care in 1L mUC. Translational studies from our center show Nectin-4 expression in many BCVH pts and data support immune-checkpoint inhibitor (ICI) activity in subsets of these pts. We hypothesize the presence of clinical activity of this combination in BCVH. Therefore, we designed this trial to assess the efficacy and safety of EV+pembro in locally advanced or metastatic BCVH (mBCVH). **Methods:** This is a Phase II, open-label, single-center trial at the Winship Cancer Institute of Emory University (NCT05756569) for pts with mBCVH. Pts will receive pembro 200mg IV on Day 1 and EV 1.25mg/Kg IV on Days 1 and 8 of a 21-day cycle for up to two years. The eligibility criteria include histologically confirmed variant histology or non-urothelial bladder cancer of epithelial origin including squamous cell carcinoma and adenocarcinoma (according to the WHO 2016 Classification), ECOG 0-1, and any line of therapy. Pts with neuroendocrine bladder cancer, non-epithelial cancers (e.g. sarcoma, lymphoma), prior ICI and/or EV treatment are excluded. Overall response rate (ORR) per RECIST 1.1 is the primary outcome and will be tested using Simon's two-stage design (n=25). The first interim analysis is planned after 15 patients. The desirable target is ORR≥30% relative to a null hypothesis of ORR ≤10%. This statistical design yields a type I error rate of 0.05 and a power of 80% for a true ORR≥30%. Key secondary outcomes include OS, progression-free survival, duration of response, and incidence of adverse events per CTCAE v5.0. Correlative biomarker analyses using blood- and tissue-based assays will be conducted during screening and at disease progression. The trial is currently open for enrollment. Clinical trial information: NCT05756569. Research Sponsor: Astellas and Seagen are providing funding and enfortumab vedotin drug support; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, is providing pembrolizumab drug support.

TPS4616 Poster Session

Phase 3 study of disitamab vedotin with pembrolizumab vs chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma that expresses HER2 (DV-001).

Matt D. Galsky, Enrique Grande, Andrea Necchi, Alexandra Drakaki, Yohann Loriot, Sonia Franco, Mari Ichimaru, Wei Zhang, Thomas Powles; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Medical Oncology Department, MD Anderson Cancer Center Madrid, Madrid, Spain; Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy; Division of Hematology/Oncology, UCLA David Geffen School of Medicine, Los Angeles, CA; Institut de Cancérologie Gustave Roussy, Villejuif, France; Merck & Co., Inc., Rahway, NJ; Pfizer Inc., San Francisco, CA; Pfizer Inc., Bothell, WA; Barts Health NHS Trust, London, United Kingdom

Background: Platinum-based chemotherapy (chemo) has been the standard first-line (1L) therapy for locally advanced or metastatic urothelial carcinoma (la/mUC). Recently, enfortumab vedotin, a nectin-4-directed antibody-drug conjugate (ADC) with a monomethyl auristatin E (MMAE) payload, plus pembrolizumab (pembro) showed improved survival over chemo. Human epidermal growth factor receptor 2 (HER2) expression (immunohistochemistry [IHC] 1+-3+) has been reported in approximately half of all patients (pts) across tumor types, including UC, and is a biomarker that may be associated with poor outcomes. Disitamab vedotin (DV; RC48-ADC) is an investigational ADC comprising a fully humanized HER2-directed monoclonal antibody, disitamab, conjugated to MMAE via a protease-cleavable mc-vc linker. DV elicits antitumor activity through multimodal mechanisms of action, including MMAE-mediated direct cytotoxicity, bystander effect, and immunogenic cell death. DV has shown encouraging activity with a manageable safety profile in pts with la/mUC—as a single agent in a HER2-expressing post-platinum setting (IHC 3+/2+; ORR, 50.5%; median [m]PFS, 5.9 months; mOS, 14.2 months) and in combination with a programmed cell death protein 1 (PD-1) inhibitor in all comers (ORR, 76.0% in treatment-naive pts; 83.3%, 64.3%, and 33.3% in HER2 IHC 3+/2+, IHC 1+, and IHC 0 subgroups, respectively). Improved outcomes observed with an MMAE payload plus PD-1 inhibition across the ADC landscape, along with DV data, provide a robust rationale for this phase 3 trial of DV with pembro in the 1L setting for HER2-expressing la/mUC.
Methods: DV-001 (NCT05911295) is an open-label, randomized, multicenter, controlled phase 3 trial evaluating DV with pembro vs chemo in pts with previously untreated HER2-expressing la/mUC. Pts will be randomized 1:1 to Arm A or B. Pts in Arm A will receive DV IV every 2 weeks and pembro IV every 6 weeks. Treatment will continue until disease progression or intolerable toxicity; pembro will be administered for a maximum of 18 6-weekly infusions (approximately 2 years). Pts in Arm B will receive platinum-based chemo with gemcitabine IV on Days 1 and 8 of every 3-week cycle, and either cisplatin or carboplatin on Day 1 of every 3-week cycle for 4-6 cycles. Maintenance therapy with avelumab after completion of chemo may be given to eligible pts where approved and available. Pts must have previously untreated la/mUC, measurable disease per RECIST v1.1, ECOG PS of 0-2 and must be eligible for platinum-based chemo. HER2 expression must be determined using the VENTANA 4B5 HER2 IHC Assay centrally and using the most recent archival or fresh tumor sample. Primary endpoints include PFS per blinded independent central review and OS. Enrollment is ongoing in the US, Canada, and Australia and is planned globally. Clinical trial information: NCT05911295. Research Sponsor: This study was sponsored by Seagen, which was acquired by Pfizer in Dec. 2023.

TPS4617 **Poster Session**

A phase III randomized trial of eribulin (E) with gemcitabine (G) vs standard of care (SOC) for patients (pts) with metastatic urothelial carcinoma (mUC) refractory to or ineligible for PD/PDL1 antibody (Ab): SWOG S1937 updated design.

Sarmad Sadeghi, Melissa Plets, Primo N Lara Jr., Catherine Tangen, Stephanie A. Berg, Jason R Brown, Rick Bangs, Darrell Nakagawa, Siamak Daneshmand, Ian M. Thompson Jr., Thomas W. Flaig, Daniel P. Petrylak, Seth P. Lerner; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA; University of California, Davis Comprehensive Cancer Center, Sacramento, CA; Fred Hutchinson Cancer Research Center, Seattle, WA; Dana-Farber Cancer Institute, Boston, MA; University Hospitals Seidman Cancer Center, Cleveland, OH; SWOG Cancer Research Network, San Antonio, TX; Swog Gu Bladder Patient Advocate, Schaumburg, IL; Institute of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA; UT Health San Antonio, San Antonio, TX; University of Colorado Anschutz Medical Campus, Aurora, CO; Yale School of Medicine, New Haven, CT; Baylor College of Medicine, Houston, TX

Background: UC is 2nd most common genitourinary cancer. Enfortumab vedotin (EV) + pembrolizumab became a SOC in 2023 in frontline mUC setting. In previously treated mUC setting, erdafitinib is approved for pts with FGFR alterations, while all pts have the option of sacituzumab govitecan (SG) with objective response rate (ORR) of 27% (N=113). A phase I/II CTEP study of eribulin (E) for mUC established the activity of E with ORR of 37.5% and a median progression free survival (PFS) of 4.1 months (mo) and median overall survival (OS) of 9.5 mo (N=150). A phase II CTEP study of gemcitabine-eribulin (GE) in cisplatin ineligible mUC showed ORR of 50%, median OS of 11.9 mo and median PFS of 5.3 mo (N=24). The most common Grade 3-4 toxicities included: neutropenia 63%, anemia and fatigue 29%. Pts with liver metastases benefited from therapy with 71% ORR (n=7) for GE vs 24% for E (n=49). This trial has now been amended to account for first-line treatment changes and to include SG as a control arm option.
Methods: This is an updated phase III, randomized trial comparing GE vs. SOC (SG, docetaxel, paclitaxel, or G monotherapy). E is given at 1.4mg/m2 on day (D) 1 and 8 of a 21 D cycle and G is given at 1000 mg/m2 on D1 and D8. SOC follows approved dosing. There is no limit to the number/sequence of prior regimens. In brief, all pts must have: received systemic therapy with EV; received PD1/PDL1 Ab or be deemed ineligible for PD1/PDL1 Ab. The study seeks to find at least a 50% increase in the primary endpoint of OS (Hazard Ratio (HR) = 0.667). The secondary endpoints include ORR, and progression free survival (PFS). One-sided 0.05 type I error to account and 80% power to detect a 50% improvement in OS. We require 92 eligible pts in each arm for a total of 184. The amended and restructured study was approved in January of 2024.
Funding: National Institutes of Health/National Cancer Institute grants U10CA180888, U10CA180819. Eribulin is provided by Eisai. Clinical trial information: NCT04579224. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180888, U10CA180819.

TPS4618 **Poster Session**

Sacituzumab govitecan (SG) plus enfortumab vedotin (EV) for metastatic urothelial carcinoma (mUC) treatment-experienced (DAD) and with pembrolizumab (P) in treatment naïve UC (DAD-IO).

Bradley Alexander McGregor, Lucia Kwak, Guru P. Sonpavde, Stephanie A. Berg, Toni K. CHOUEIRI, Joaquim Bellmunt, Charlene Mantia; Lank Center for Genitourinary Oncology, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; AdventHealth Cancer Institute, Orlando, FL; The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: In the DAD study (NCT04724018) the combination of SG+EV demonstrated favorable safety determining a maximum tolerated dose of 10 mg/kg and 1.25 mg/kg IV D1,8 every 21 days along with encouraging efficacy in treatment resistant mUC as evidenced by an objective response rate (ORR) of 70% in 23 evaluable patients. Given cumulative toxicities and efficacy across dose levels, the recommended phase 2 dose was SG 7.5 mg/kg and EV 1.25 mg/kg D1,8 of 21-day cycle. As EV+P is now a standard of care for front line urothelial carcinoma, NCT04724018 was amended to include 2 cohorts of distinct patient populations; one expanding SG+EV (DAD) and a second exploring the SG+EV+P (DAD-IO) combination. **Methods:** In DAD cohort, patients with mUC progressing on platinum and immunotherapy or on one line of therapy receive SG 7.5 mg/kg + EV 1.25 mg/kg intravenously (IV) on day(D)s 1 and 8 every 3 weeks (1 cycle) until progression or intolerable toxicities. In DAD-IO cohort, patients with treatment naïve mUC are given SG 7.5 mg/kg+EV 1.25 mg/kg IV D1, 8 of a 21-day cycle with P 200 mg every 3 weeks or 400 mg every 6 weeks per investigator discretion. In both cohorts, prophylactic granulocyte colony stimulating factor (GCSF) support is given per supportive care guidelines with cycle 1. Following first dose on trial, SG and EV can be reduced and held independently for toxicity with reductions of SG to 5 mg/kg, and EV to 1, 0.75 and 0.5 mg/kg. P dose reductions are not allowed but can be held as needed for immune related adverse events. Laboratory evaluation is performed on days 1 and 8 every cycle. Imaging is performed at baseline and every 6 weeks for the first 4 cycles followed by every 9 weeks thereafter. In both cohorts, the primary endpoint is RECIST 1.1 ORR with secondary endpoints being progression free survival, overall survival, and safety. DAD aims to enroll 41 eligible patients, assuming an ORR of 65% for EV+SG, to detect a 25% improvement with over 90% power at a one-sided type I error rate of 0.05 using a single-stage exact one-sample binomial design; ^{3} 23 responses would rule out a null of 40% ORR. DAD-IO plans to enroll 41 eligible patients, assuming an ORR of 75% for SG+EV+P to detect a 20% improvement with 90% power at a one-sided type I error rate 0.09 based on a Simon optimal two-stage design. If ^{3} 11 responses are observed in the first 18 patients, an additional 23 patients will be enrolled. At least 27 responses among a total of 41 will be needed to confirm its efficacy. The study includes a 12-patient safety lead in using a Bayesian toxicity monitoring. If ≤2 dose limiting toxicities (DLTs) occur in the first 6 patients, the next 6 are enrolled. The study halts if ≥5 DLTs occur among 12 evaluable patients. Clinical trial information: NCT04724018. Research Sponsor: Gilead.

	DAD	DAD-IO
N	41	41
Prior treatment	≥1 line of therapy	None
Intervention	SG+EV	SG+EV+P

TPS4619 Poster Session

A phase 2/3 study of Bicycle toxin conjugate BT8009 targeting nectin-4 in patients with locally advanced or metastatic urothelial cancer (la/mUC): Duravelo-2.

Yohann Loriot, Arlene O. Siefker-Radtke, Terence W. Friedlander, Andrea Necchi, Alexander Z Wei, Srikala S. Sridhar, Benjamin Garmezy, Santiago Arroyo, Emma Gartside, Jie Liu, Carly Campbell, Justin Bader, Daniel P. Petrylak; Gustave Roussy, University Paris Saclay, Villejuif, France; The University of Texas MD Anderson Cancer Center, Houston, TX; University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, Milan, Italy; Columbia University Irving Medical Center, New York, NY; Princess Margaret Cancer Center, Toronto, ON, Canada; Sarah Cannon Research Institute, Nashville, TN; Bicycle Therapeutics, Cambridge, MA; BicycleTx Ltd, Cambridge, United Kingdom; Yale School of Medicine, New Haven, CT

Background: BT8009 is a Bicycle toxin conjugate (BTC), comprising a highly selective bicyclic peptide targeting nectin-4 linked to the cytotoxin monomethyl auristatin E (MMAE) via a cleavable linker. Nectin-4 is an adhesion molecule commonly expressed in many tumor types, including urothelial cancer (UC), and is a validated therapeutic target (Hoffman-Censits 2021). BT8009 has a low molecular weight and short plasma half-life, with potential to rapidly penetrate solid tumors and reduce toxicity by minimizing exposure to normal tissue (Rigby 2022). Results from the ongoing phase 1/2 clinical trial of BT8009 (NCT04561362) indicate preliminary antitumor activity and a tolerable safety profile in patients (pts) with advanced malignancies including UC (Baldini 2023). This global, open label, phase 2/3 multicenter adaptive study aims to evaluate the safety and efficacy of BT8009 as monotherapy, or combined with pembrolizumab (pembro), vs chemotherapy in pts with locally advanced or metastatic UC (la/mUC) (NCT06225596/BT8009-230; Duravelo-2). **Methods:** The trial will enroll up to 956 adult pts in 2 cohorts. Cohort 1 will include n≤641 previously untreated pts eligible for platinum-based chemotherapy. Cohort 2 will include n≤315 pts with ≥1 prior systemic therapy, excluding enfortumab vedotin or other MMAE-based therapy. Pts must have la/mUC of the renal pelvis, ureter, bladder, or urethra, ECOG performance status ≤2 (Cohort 1) or ≤1 (Cohort 2), and adequate organ function. Cohort 1 will be randomized 1:1:1 to receive: 1) BT8009 5 mg/m^2 on days (D)1, 8, and 15 + pembro 200 mg on D1; 2) BT8009 6 mg/m^2 on D1 and 8 + pembro 200 mg on D1; or 3) chemotherapy (gemcitabine + cisplatin / carboplatin, followed by avelumab maintenance). Cohort 2 will be randomized 1:1 to receive: 1) BT8009 5 mg/m^2 on D1, 8, and 15 or 2) BT8009 6 mg/m^2 on D1 and 8. Cycle lengths will be 21D (28D for avelumab). After 30 pts in each dose arm have 9 weeks follow-up, an interim analysis will determine the optimal dose of BT8009 + pembro (Cohort 1) or BT8009 monotherapy (Cohort 2) to be used for the rest of the study. An additional Cohort 2 arm, optimal dose of BT8009 + pembro, will open after completion of the interim analysis. Discontinuation criteria include planned completion of therapy, progressive disease, and intolerable toxicity. Primary endpoints are progression-free survival (PFS; Cohort 1) and objective response rate (ORR; Cohort 2) assessed by blinded independent central review. Secondary endpoints are ORR (Cohort 1), PFS (Cohort 2), and overall survival, duration of response, disease control rate, safety/tolerability, and health-related quality of life (Cohorts 1 and 2). Pharmacokinetics, incidence/titers of antidrug antibodies, and tumor/peripheral biomarkers are exploratory endpoints. Efficacy endpoints will be assessed per RECIST v1.1. This study is actively recruiting. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

TPS4620 Poster Session

INSIGHT-005: A new stratum of the explorative, open-labeled, phase I INSIGHT study to evaluate the feasibility and safety, as well as preliminary efficacy, of subcutaneous injections with IMP321 (eftilagimod alpha) in combination with PD-L1 inhibitor (avelumab) for metastatic or unresectable locally advanced urothelial carcinoma (UC)—IKF-s614.

Igor Tsaur, Maximilian Peter Johannes Karl Brandt, Eray Goekkurt, Viktor Grünwald, Daniel Pink, Florian Roghmann, Martin Sebastian, Friedemann Zengerling, Sabine Beck, Christine Koch, Johanna Riedel, Ulas Tenekeci, Daniel Wilhelm Mueller, Salah-Eddin Al-Batran, Thorsten Goetze; Universitätsklinik Tübingen, Klinik für Urologie, Tuebingen, Germany; Department of Urology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany; Hematology Oncology Practice Eppendorf (HOPE) and University Cancer Center Hamburg (UCCH), Hamburg, Germany; University Hospital Essen, West German Cancer Center, Interdisciplinary Genitourinary Oncology, Clinic for Internal Medicine and Department of Urology, Essen, Germany; Klinik und Poliklinik für Innere Medizin C, Hämatologie und Onkologie, Transplantationszentrum, Palliativmedizin, Universität Greifswald and Klinik für Hämatologie, Onkologie und Palliativmedizin-Sarkomzentrum, HELIOS Klinikum Bad Saarow, Bad Saarow, Germany; Department of Urology, University Hospital of Ruhr-University Bochum, Marien Hospital, Herne, Germany; Goethe University Frankfurt, University Hospital, Medical Department 2, Frankfurt Am Main, Germany; Department of Urology und Paediatric Urology, Hospital University of Ulm, Ulm, Germany; Frankfurter Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany; Frankfurter Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest; Frankfurt University Clinic, Dept. of Gastroenterology, Hepatology and Endocrinology; Frankfurt Cancer Centre (UCT), Frankfurt Am Main, Germany; Krankenhaus Nordwest, University Cancer Center Frankfurt and Frankfurter Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany; Krankenhaus Nordwest Frankfurt, University Cancer Center (UCT) Frankfurt, Frankfurter Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany

Background: UCs are the 6th most common malignancies in the Western world being localized in the upper (5-10%) or the lower (90-95%) urinary tract. Metastatic UC (mUC), which accounts for 5% of all cases, is associated with a dismal prognosis and prompt progression. So far, the 1st line therapy for mUC encompassed platinum-based combination regimens. Recent data indicate beneficial patient treatment with immune checkpoint inhibitors. Thus, avelumab was approved for maintenance therapy after progression-free platinum-based chemotherapy for locally advanced (LA) or mUC. Further immune checkpoint inhibitors (e.g. pembrolizumab, atezolizumab, nivolumab) achieved approval or showed promising results for treatment of different patient populations. Eftilagimod alpha (efti) is a soluble LAG-3 fusion protein and a MHC class II agonist activating APCs followed by CD8 T-cell activation. The combination of efti with PD-1/PD-L1 blockade is not yet available and is proposed to enhance efficacy. Based on previous results from the INSIGHT trial and change in treatment landscape we hypothesize that combining avelumab and efti will display clinically relevant efficacy in unresectable LA UC or mUC subgroups with acceptable toxicity. **Methods:** INSIGHT-005 is a new stratum within the investigator-initiated INSIGHT phase I platform trial ongoing at multiple sites (n=9) in Germany. Patients with unresectable LA UC or mUC will receive efti in combination with avelumab. 30 patients will be enrolled in 3 subgroups: I) Previously untreated, eligible for platinum-based therapy, with PD-L1 CPS≥10; II) Previously untreated, not-eligible for platinum-based therapy, irrespective of the PD-L1 status; III) Suffered disease progression after platinum-based chemotherapy for metastatic disease and did not receive avelumab maintenance therapy, irrespective of the PD-L1 status. Enrolled patients will receive avelumab 800 mg i.v. and efti 30 mg s.c. on the same day Q2W for a maximum of 24 cycles. Tumor evaluation will be performed via CT or MRI every 8 weeks. The primary endpoint of this study is to explore feasibility, safety, and preliminary efficacy of efti when added to avelumab in unresectable LA UC or mUC. Secondary endpoints include safety and efficacy parameters as defined by objective response, time to and duration of response and PFS according to RECIST 1.1, OS and biomarker analyses. First patient was enrolled on 2023-11-29. Currently, recruitment is ongoing. ClinicalTrials.gov ID: NCT03252938 Clinical trial information: NCT03252938. Research Sponsor: Immutep S.A.S; Merck KGaA, Darmstadt, Germany.

TPS4621 **Poster Session**

Use of gene expression patterns to identify unique molecular subtypes in muscle invasive bladder cancer: GUSTO.

Simon J. Crabb, Syed A. Hussain, Jamie B. Oughton, Jayne Swain, David A. Cairns, Michelle Collinson, Gemma Ainsworth, Dominic McCready, Jon Griffin, Paul Heath, Lewis Quayle, Jenny Down, Dennis Wang, Allen Knight, Ewan Gibb, Elai Davicioni, Yang Liu, James W.F. Catto; University of Southampton Faculty of Medicine, Durley, United Kingdom; University of Sheffield, Sheffield, United Kingdom; Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom; Imperial College London, London, United Kingdom; Action on Bladder Cancer, Tetbury, United Kingdom; Veracyte, Inc, Vancouver, BC, Canada; Decipher Biosciences, San Diego, CA; Veracyte, Inc, San Francisco, CA

Background: Muscle invasive bladder cancer (MIBC) is an aggressive disease with poor survival rates that are not improving. Curative treatment includes systemic neoadjuvant chemotherapy prior to radical cystectomy and adjuvant immunotherapy. However, many patients do not respond to chemotherapy or immunotherapy. Histologically similar MIBCs can be classified using gene expression patterns into unique molecular subtypes. Retrospective studies have shown that molecular subtypes each have unique biology and consequently respond differently to treatment. The GUSTO trial tests the hypothesis that outcomes can be optimized through subtype-guided allocation. **Methods:** Eligible participants are those with confirmed non-metastatic MIBC, an ECOG performance status 0-1, being considered for cisplatin-based neoadjuvant chemotherapy and radical cystectomy. Formalin-fixed diagnostic (TURBT) tumor samples undergo gene expression microarray analysis and characterization using the GUSTO Classifier (consisting of the Veracyte Decipher assay and TCGA_2017 classification system) to determine the molecular subtype: basal, neuronal, luminal infiltrated, luminal or luminal papillary. A total of 320 eligible patients (T2-4a N0 M0 or T(any) N1 M0 MIBC) will be randomized 1:1 to either standard of care treatment (neoadjuvant cisplatin and gemcitabine) or subtype-guided treatment (basal and neuronal subtypes - neoadjuvant cisplatin, gemcitabine, durvalumab and tremelimumab and adjuvant durvalumab; luminal infiltrated - neoadjuvant durvalumab and tremelimumab and adjuvant durvalumab; luminal and luminal papillary - proceeding directly to radical cystectomy). Sites are notified when a patient has been assigned a molecular subtype. Patients and sites in the standard of care arm remain blind to the genomic subtype. The trial has three stages: Stage 1 (after 6 months of recruitment) will assess feasibility of recruitment and molecular subtyping in clinical timelines. Outcomes include recruitment rate, time to, and success of subtype allocation. Stage 2 (after 24 months of recruitment) will confirm recruitment feasibility and assess sample size assumptions. Outcomes are recruitment numbers, distributions of subtypes, and pathological complete response (pCR) in the standard of care arm. A re-estimation of the sample size for stage 3 will be considered. Stage 3 (after 12 months post-cystectomy for the last participant randomized) will assess treatment outcomes using this stratified approach. The primary outcome for Stage 3 is the rate of pCR in each molecular subtype within the experimental arm. Progression between trial stages will be dependent upon achieving pre-defined criteria. Recruitment began in September 2023. The study will open the first 20 sites ready to proceed and is accepting expressions of interest. Clinical trial information: 17378733. Research Sponsor: NIHR EME; AstraZeneca.

TPS4622 Poster Session

ENLIGHTED phase 3 study: Efficacy and safety of padeliporfin vascular targeted photodynamic therapy (VTP) for treatment of low-grade upper tract urothelial cancer (LG UTUC).

Vitaly Margulis, Ronald P. Kaufman Jr., Gautier Marcq, Neal D. Shore, Marc Colombel, Edward M. Uchio, Sarah P. Psutka, Marcos Aller, Steffen Rausch, Carles Raventos, Asaf Shvero, Axelle Mroz, Natalia Kudinova, Yaniv Cohen, Inna Krasnopolskaya, Genia Alpert, Avigdor Joshua Scherz, Jonathan Coleman; Department of Urology, University of Texas Southwestern, Dallas, TX; Albany Medical College, Albany, NY; Lille University Hospital, Lille, France; Carolina Urologic Research Center and GenesisCare US, Myrtle Beach, SC; Hopital Edouard Herriot, Lyon, France; University of California, Irvine, Irvine, CA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Hospital Universitario de A Coruna, Coruna, Spain; Department of Urology, Eberhard Karls University, Tübingen, Germany; Department of Urology, Vall d' Hebron University Hospital, Barcelona, Spain; Deptartment of Urology, "Chaim Sheba" Medical Center, Ramat Gan, Israel; Steba/Impact Biotech, Versailles, France; Steba/Impact Biotech, Ness Ziona, Israel; Weizmann Institute of Science, Department of Plants and Environmental Sciences, Rehovot, Israel; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Padeliporfin VTP has demonstrated safety and efficacy for UTUC treatment in a Phase 1 study (NCT03617003). Padeliporfin VTP is a combination product: a drug, padeliporfin administered IV; a device: a laser light delivery system/laser-source of light emitting near-infrared (NIR) light at 753nm; and an optic fiber delivering the light endoluminally to the vicinity of UTUC tumors within the collecting system. We report the preliminary efficacy and safety outcomes of Padeliporfin VTP for Treatment of LG UTUC in ENLIGHTED, a Phase 3 trial (NCT04620239). **Methods:** This is an open-label phase 3 study from USA, EU and Israel. Key inclusion criteria is up to 2 biopsy-proven LG UTUC with index tumor ≤15mm in the kidney and≤20mm in the ureter with an absence of high-grade cells on cytology. VTP is performed via retrograde upper tract endoscopy under anesthetic and low light conditions, Padeliporfin is injected IV and a laser light diffuser fiber 20-40 mm is positioned in proximity of the tumor through the scope. After Padeliporfin injection, the laser fiber is illuminated for 10 min. The fiber can be repositioned to provide up to 3 treatments within the upper tract. Patients are treated in two phases: Induction(ITP) and Maintenance Treatment Phases (MTP). ITP consists of 1-3 VTPs provided at 4-week intervals until achieving complete response (CR) or treatment failure. Patients achieving CR will proceed to the MTP and be followed with endoscopic evaluation every 3 months with VTP provided for recurrent tumors only up to 12 months. Patients with high-grade recurrences will be deemed treatment failures and removed from the study to standard of care treatment. Patients completing the MTP, will be followed for an additional 48 months for long-term outcomes. Primary outcome is CR on endoscopic evaluation and selective cytology at the time of primary response evaluation (28 ± 3 days post last treatment) during padeliporfin VTP ITP. A total of 100 patients are to be enrolled. As of 21 Jan 2024, 17 patients have been treated. 13 patients completed ITP and had CR 10/13 (77%) and PR 3/13 (23%). Patients baseline characteristics: age 67±12 years; gender: 9(53%) males and 8(47%) females; tumors location: 5(29%) in ureter, 13(76%) in the kidney; number of tumors: 7(41%) 2 tumors, 10(59%) 1 tumor. The most frequent treatment related adverse events were: flank pain 17%, vomiting 8%, fatigue 8%, nausea 6%, hematuria 6%, all Grade 1-2, resolved within few days. Grade 3 serious adverse events 9% (flank pain, hypertension, renal colic, urinary tract infection) were resolved within 2-7 days. To date Padeliporfin VTP has shown evidence of safety and efficacy with preliminary data that is consistent with prior experience. Recruitment for the ENLIGHTED trial is ongoing with results expected to provide basis for approval of a new therapy that clinically benefits pts. Clinical trial information: NCT04620239. Research Sponsor: None.

TPS4623 Poster Session

SOGUG-NEOWIN: A phase 2, open-label, multi-centre, multi-national interventional trial evaluating the efficacy and safety of erdafitinib (ERDA) monotherapy and ERDA and cetrelimab (CET) as neoadjuvant treatment in patients with cisplatin-ineligible muscle-invasive bladder cancer (MIBC) whose tumours express FGFR gene alterations.

Syed A. Hussain, Yohann Loriot, Guillermo de Velasco, Andrea Necchi; University of Sheffield, Sheffield, United Kingdom; Université Paris-Sud, Université Paris-Saclay, Gustave Roussy, Villejuif, France; Medical Oncology Department, Hospital Universitario 12 De Octubre, Madrid, Spain; Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, Milan, Italy

Background: The standard treatment for nonmetastatic MIBC is neoadjuvant cisplatin-based therapy followed by radical cystectomy (RC). However, many patients are ineligible for cisplatin. Immune checkpoint inhibitors (ICIs) have changed the treatment landscape for metastatic urothelial cancer (mUC), including for cisplatin-ineligible patients. Based on these results, ICIs are being explored as neoadjuvant treatment in resectable UC with preliminary data suggesting antitumour activity. ERDA is a Fibroblast Growth Factor Receptor (FGFR) inhibitor, which has shown efficacy in advanced UC with select FGFR2/3 mutations/fusions. ERDA plus cetrelimab demonstrated clinically meaningful activity in patients with newly diagnosed FGFR-altered mUC in the phase 2 NORSE trial. We hypothesize that ERDA plus cetrelimab will improve the pathological complete response (pCR) rate in patients with FGFR+ MIBC who are candidates for RC and are ineligible for or refuse neoadjuvant cisplatin-based therapy. **Methods:** SOGUG-NEOWIN is a prospective, non-comparative, open label, multicentre, international trial to assess the efficacy of 9 or 12 weeks of neoadjuvant ERDA (cohort 1) or the combination of cetrelimab and ERDA (cohort 2) in patients with MIBC (cT2-Ta N0/1 M0) and FGFR alterations. Key eligibility criteria include ECOG PS 0-1; pure or predominant UC histology; decline or ineligible for cisplatin-based chemotherapy as defined by one of the following criteria: impaired renal function (GFR $<$ 60 mL/min), $\geq$ grade 2 hearing loss, or $\geq$ grade 2 peripheral neuropathy; patients are considered fit for cystectomy; no prior FGFR-targeted or anti-PD-(L)1 therapy; no prior systemic therapy, radiation or surgery (except TURBT or biopsies) for bladder cancer; prior BCG was allowed if completed $\geq$ 6 weeks before initiation of study treatment; no current retinopathy. A total of 45 patients will be allocated to each cohort by a centralized system. Co-primary endpoints are pCR rate and percentage of pathological downstaging response ($<$ypT2). Secondary endpoints include event-free survival, overall survival, overall response rate, safety, tolerability, and delay to surgery. Biomarkers of response and resistance will be assessed using baseline archival tissues, blood and urine. Quality of life (QoL) will be assessed using FACT-Bl and EQ-5D-5L. Tumour response assessment via PET-MRI will be performed in a subset of patients. The trial is approved in 4 countries. The first patient was included on 31-Jan-2024. This trial would be the first to systematically address whether ERDA $\pm$ cetrelimab improves pCR in patients with FGFR-positive MIBC. (EudraCT 2022-002586-15). Clinical trial information: 2022-002586-15. Research Sponsor: Janssen.

TPS4624 Poster Session

NETOS: A personalized approach of neoadjuvant therapy, including INCB099280 monotherapy and bladder preservation, for muscle-invasive urothelial bladder carcinoma (MIBC) with ctDNA monitoring.

Andrea Necchi, Valentina Tateo, Antonio Cigliola, Chiara Mercinelli, Damiano Patanè, Marco Moschini, Renzo Colombo, Maurizio Colecchia, Giorgio Brembilla, Alberto Briganti, Francesco Montorsi; Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital, Milan, Italy; Medical Oncology Department, IRCCS San Raffaele Hospital, Milan, Italy; IRCCS San Raffaele Hospital, Milan, Italy; Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy; Urology Unit, IRCCS Ospedale San Raffaele, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy; Department of Radiology, IRCCS San Raffaele Hospital, Milan, Italy; Vita-Salute San Raffaele University, Milano, Italy

Background: MIBC is a systemic disease as >40% of patients (pts) ultimately develop recurrence after radical cystectomy (RC). For pts who cannot receive or refuse cisplatin-based chemotherapy there is no standard-of-care neoadjuvant therapy. Single-agent pembrolizumab, given neoadjuvantly in patients with T2-4N0M0 MIBC, was effective in PURE-01 trial. A proportion of these pts refused RC and were cured with pembro and redo transurethral resection of the bladder tumor (reTURBT; Bandini et al. PMID: 32979511). There are increasing concerns by the pts related to the need to undergo RC whenever they achieve a clinical complete response (cCR) with TURBT and systemic therapy. INCB099280 is a potent, orally bioavailable, selective, small molecule that targets PD-L1 that is being developed for the treatment of advanced malignant diseases. A phase 1, dose-escalation and expansion study is ongoing in pts with select advanced solid tumors (NCT04242199); safety and preliminary efficacy results have been reported (Prenen et al. ESMO-IO 2023). Our hypothesis is that INCB099280 can be offered in biomarker-selected pts as a maintenance therapy instead of any additional treatment, provided that a cCR after the induction phase is obtained. **Methods:** Pts should have a predominant urothelial carcinoma (UC) histology, have a clinical stage T2-T4N0M0 MIBC, be ineligible for or refuse to receive cisplatin-based chemotherapy. The study will also select pts with a circulating tumor DNA (ctDNA)-positive test (Signatera ctDNA assay) and will be staged with pelvic MRI. Pts will receive 12 weeks of INCB099280 at the dose of 400 mg twice daily (BID), continuously. Restaging will be planned with ctDNA, imaging and reTURBT. Pts who will achieve a cCR (i.e., no evidence of residual disease at the histological examination, clearance of ctDNA and the evidence of no residual detectable disease at cross-sectional imaging, evaluated locally) will receive additional INCB099280 400 mg BID for a maintenance period of 12 months. Pts with evidence of high grade or infiltrating residual disease will be discontinued from the study. Those with a Ta/T1-low grade disease will be managed according to physician's preference: they may be eligible to continue within the study protocol and receive maintenance INCB099280 400 mg BID for a total period of 12 months. The primary endpoint is the proportion of cCR and the study is planned according to A'Hern one-stage binomial design, with H0 ≤5% and H1 ≥20%, 5% one-sided Alpha, 80% power and 10% drop-out rate. The overall sample size Will be of 30 pts. Secondary endpoints will include safety (CTCAE v.5.0), event-free survival, bladder-intact overall survival (OS) and OS (EUCT number: 2024-511029-73-00). Clinical trial information: 2024-511029-73-00. Research Sponsor: Incyte.

TPS4625 **Poster Session**

Adjuvant or rescue disitamab vedotin (RC48-ADC) for high-risk non-muscle invasive bladder cancer with HER2 overexpression: A phase II multi-center study.

Junru Chen, Haoyang Liu, Qiyu Zhu, Chenhao Xu, Qiang Wei, Jiyan Liu, Zhenhua Liu, Pengfei Shen, Yige Bao, Peng Zhang, Banghua Liao, Jin Yao, Ni Chen, Kaijie Wu, Xiaodong Liu, Hao Zeng; West China Hospital of Sichuan Univertity, Chendu, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; Department of Urology, West China Hospital, Sichuan University, Chengdu, China; West China Hospital, Sichuan University, Chengdu, China; Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China; Department of Radiology, West China Hospital, Sichuan University, Chengdu, China; Department of Pathology, West China Hospital, Sichuan University, Chengdu, China; Department of Urology, The First Affiliated Hospital of Xi'an Jiaotong University, Xian, China; The First Affiliated Hospital of Kunming Medical University, Kunming, China

Background: Non-muscle invasive bladder cancer (NMIBC) comprises approximately three-quarters of newly diagnosed cases of bladder cancer. Based on the risk of disease progression, NMIBC is categorized into low, intermediate, and high risk, with high-risk NMIBC patients facing a 5-year disease progression rate of up to 40%. The current standard treatment for high-risk NMIBC involves transurethral resection of the bladder tumor (TURBT) combined with intravesical Bacillus Calmette-Guérin (BCG) instillation as adjuvant therapy. In cases of BCG instillation treatment failure, the standard approach is radical cystectomy. Multiple studies have reported HER2 positivity in 20-44% of NMIBC cases, and HER2 overexpression (immunohistochemistry $\geq$2+) is closely linked to the progression and adverse prognosis of bladder cancer. Consequently, HER2 may serve as a novel therapeutic target for bladder cancer. Disitamab Vedotin (DV; RC48-ADC) is an antibody-drug conjugate (ADC) comprising a fully humanized HER2-directed monoclonal antibody conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable mc-vc linker. Results from a Phase II clinical trial (NCT03507166) suggest that Disitamab Vedotin exhibits favorable efficacy and safety in HER2-positive metastatic urothelial carcinoma patients who have previously failed chemotherapy. This clinical trial aims to investigate the efficacy and safety of RC48-ADC as adjuvant or rescue therapy for high-risk NMIBC with HER2 overexpression and to explore molecular biomarkers predicting the efficacy of RC48-ADC. **Methods:** This multicenter, Phase II clinical trial will enroll two cohorts: Cohort A, consisting of 52 patients undergoing first-line adjuvant therapy, and Cohort B, with 25 patients receiving rescue therapy after BCG instillation failure, both exhibiting HER2 overexpression in high-risk NMIBC. Following the Simon two-stage optimal design, the first stage will involve enrolling 19 patients in Cohort A and 12 patients in Cohort B. After safety and baseline assessments, both cohorts will undergo six cycles of treatment with RC48-ADC (120 mg intravenous infusion every two weeks), totaling 12 weeks of treatment. Primary endpoints include safety, 12-month recurrence-free rate (Cohort A), and 3-month clinical complete response rate (Cohort B). Secondary endpoints encompass the 6-month recurrence-free rate (Cohort A), duration of response (Cohort B), recurrence-free survival, progression-free survival, overall survival, and quality of life (assessed through eEuroQoL EQ-5D and FACT-BI). Additionally, exploratory endpoints will investigate the relationship between biomarkers in tumor tissues, blood, and urine, and treatment efficacy. Clinical trial information: NCT05996952. Research Sponsor: None.

TPS4626 Poster Session

A phase 1/2 study of EG-70 (detalimogene voraplasmid) intravesical monotherapy for patients with BCG-unresponsive non-muscle invasive bladder cancer with carcinoma in situ.

Richard Bryce, Christine Tosone, James C. Sullivan, Tammy Linback, Gary D. Steinberg; EnGene Inc., Boston, MA; RUSH University Medical College, Chicago, IL

Background: High-risk non-muscle-invasive bladder cancer (NMIBC) is treated with adjuvant intravesical Bacille Calmette-Guérin (BCG). However, approximately 50% of patients experience recurrence and/or progression after BCG treatment and are considered unresponsive. EG-70 (detalimogene voraplasmid) is an investigational drug product that was specifically engineered for intravesical administration to elicit local stimulation of anti-tumor immune responses in the bladder and drive durable efficacy in patients with BCG-unresponsive NMIBC, while mitigating the risk of systemic toxicities from immune stimulation. The phase 1 (dose-escalation) part of the first-in-human LEGEND (NCT04752722) phase 1/2, open-label, multicenter study of EG-70 in patients with high-risk BCG-unresponsive NMIBC with carcinoma *in situ* (CIS) is complete: intravesical instillation of EG-70 was well tolerated with an overall complete response (CR) rate of 73%; and the recommended phase 2 dose (RP2D) was identified. Here we describe the ongoing phase 2 part of the study, which opened to enrollment in May 2023. **Methods:** Patient eligibility criteria: age ≥18 years; ECOG PS 0−2; BCG-unresponsive NMIBC with CIS, with or without resected coexisting papillary tumors, ineligible for, or have elected not to undergo, cystectomy; satisfactory bladder function with ability to retain study drug for ≥60 minutes. Prior checkpoint inhibitor treatment is allowed if completed within 30 days before study entry. Patients are treated with EG-70 at the RP2D (800 μg in 50 mL) by intravesical administration on weeks 1, 2, 5, and 6 of a 12-week cycle, for 4 cycles in one of two cohorts: BCG-unresponsive (Cohort 1); BCG-naïve or BCG-incompletely treated (Cohort 2). Patients in either cohort who exhibit stable disease (SD) or CR at week 12 will continue treatment until week 24; patients with progressive disease (PD) will discontinue treatment. Patients who experience or maintain CR at week 24 will receive additional cycles every 12 weeks until week 48; patients with SD or PD at week 24 will discontinue treatment. Patients with PD at any time after week 24 will discontinue treatment. Phase 2 primary objective: evaluate efficacy (CR rate at week 48) and safety of EG-70. Secondary objectives: evaluate progression-free survival, CR rate at 12, 24, 36 and 48 weeks, and duration of response. The study is being conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and with the principles of the Declaration of Helsinki. All patients provide written informed consent. The ongoing, registration-enabling phase 2 portion of the LEGEND study is anticipated to recruit approximately 100 patients from sites in North America, Europe, and the Asia-Pacific region. Clinical trial information: NCT04752722. Research Sponsor: None.

TPS4627 Poster Session

SMART: A phase II study of sacituzumab govitecan (SG) with or without atezolizumab immunotherapy in rare genitourinary (GU) tumors such as small cell, adenocarcinoma, and squamous cell bladder/urinary tract cancer, renal medullary carcinoma (RMC) and penile cancer.

Andre Rashad Kydd, Elias Chandran, Nicholas I. Simon, Saad Omar Atiq, Tzu-fang Wang, Lisa M. Cordes, Elizabeth Smith, Matthew Lindsley, Lisa Ley, Salah Boudjadi, Scot Anthony Niglio, Sally Weng, Ian Stukes, Md Shahid Sarwar, Rouf Banday, Dilara Akbulut, Sandeep Gurram, Bernadette Redd, Seth M. Steinberg, Andrea B Apolo; Genitourinary Malignancies Branch, CCR, NCI, NIH, Bethesda, MD; National Cancer Institute, Bethesda, MD; New York University Grossman School of Medicine, New York, NY; Laboratory of Pathology, CCR, NCI, NIH, Bethesda, MD; Urologic Oncology Branch, CCR, NCI, NIH, Bethesda, MD; Radiology and Imaging Sciences, CCR, NCI, NIH, Bethesda, MD; Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Rare tumors of the GU tract often exhibit aggressive clinical behavior, yet lack effective standard of care treatment options. SG is an antibody-drug conjugate (ADC) targeting trophoblastic cell surface antigen 2 (Trop2) with a payload of SN-38, a topoisomerase inhibitor. SG monotherapy gained accelerated approval in pts with metastatic urothelial carcinoma (mUC) post platinum and immune-checkpoint inhibitor (ICI) therapy based on the TROPHY-U-01 trial (Tagawa S et al., JCO 2021). Atezolizumab is an anti-PD-L1 ICI approved for use in multiple solid tumors. SMART will evaluate the efficacy and safety of SG monotherapy or SG plus atezolizumab in select rare GU tumors. **Methods:** SMART is an open-label, non-randomized, Phase 2 trial. Pts must have locally advanced (unresectable) or metastatic GU tumors of the following histologies: small cell carcinoma, squamous cell carcinoma, or primary adenocarcinoma of the bladder or urinary tract, RMC, or squamous cell carcinoma of the penis. Pts may be treatment-naïve or have received any number of prior therapies; pts with small cell carcinoma must have received a platinum-based regimen. Pts treated with a PD-1/PD-L1 ICI will be assigned to Cohort A/Treatment Arm 1 and will receive SG monotherapy (10mg/kg IV, D1 and D8 of 21 day cycles). Pts without prior ICI treatment will be assigned to Cohort B/Treatment Arm 2 and will receive SG (10mg/kg IV, D1 and D8 of 21 day cycles) with concomitant atezolizumab (1200mg IV, D1 of 21 day cycles). Treatment will continue until disease progression (max duration of treatment 5 years) or intolerable side effects. The primary endpoint is objective response rate (ORR) (RECIST v1.1) for each Cohort, with restaging every 3 cycles. Secondary endpoints include safety, clinical benefit rate (CR+PR+SD), median PFS/OS for each Cohort, and ORR for each histology. Exploratory analyses include determination of baseline tumor mutation and transcriptional profile, Trop2 expression, ctDNA/CTCs, peripheral blood immune subsets and cytokine profile correlation with response, and correlation of UGT1A1 allele genotype with response and safety. This study utilizes a Simon minimax two-stage design, with enrollment of up to 43 evaluable pts (accrual ceiling of 60 pts). Cohort A will enroll 11 pts in Stage 1; if 1 or more of the first 11 pts has a response (unacceptably low rate of 5%, p0=0.05; alpha 0.10, beta=0.20), accrual will continue into Stage 2 up to 18 evaluable pts. Cohort B will enroll 16 evaluable pts in Stage 1; if 2 or more pts have a response (unacceptably low rate of 10%, p0=0.10; alpha 0.10, beta=0.10), accrual will continue in Stage 2 up to a total of 25 evaluable pts. This study is open at the NIH Clinical Center (CC); enrollment may open at 1-2 additional centers. Clinical trial information: NCT06161532. Research Sponsor: None.

TPS4628 **Poster Session**

A phase II multicenter study of enfortumab vedotin with or without pembrolizumab in rare genitourinary tumors (E-VIRTUE).

Elias Chandran, Nicholas I. Simon, Daniel da Motta Girardi, Lisa Ley, Tzu-fang Wang, Andre Rashad Kydd, Saad Omar Atiq, Salah Boudjadi, Ian Stukes, Elizabeth Smith, Dilara Akbulut, Scot Anthony Niglio, Sandeep Gurram, Marijo Bilusic, Seth M. Steinberg, Andrea B Apolo; Genitourinary Malignancies Branch, CCR, NCI, NIH, Bethesda, MD; Laboratory of Pathology, CCR, NCI, NIH, Bethesda, MD; Perlmutter Cancer Center, NYU Langone Health, New York, NY; Urologic Oncology Branch, CCR, NCI, NIH, Bethesda, MD; Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; Biostatistics and Data Management Section, OCD, NCI, NIH, Bethesda, MD

Background: Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) targeting nectin-4 with a monomethyl auristatin E (MMAE) payload, a potent microtubule inhibitor. It is standard of care (SOC) in metastatic urothelial carcinoma in combination with pembrolizumab in untreated patients and as monotherapy in post-chemotherapy, post-immune checkpoint blockade (ICB) patients. Nectin-4 expression has been retrospectively observed in 66.7-100% of urinary tract adenocarcinoma, 70-100% of urinary tract squamous cell carcinoma (SCC) (Case et al., 2022; Hoffman-Censits et al., 2021) and 36% of testicular germ cell tumors (GCTs) (The Human Protein Atlas). Metastatic urinary tract adenocarcinoma and SCC, and treatment refractory GCTs do not have an established SOC. Given the known nectin-4 expression, we hypothesize that EV with or without pembrolizumab will be active in these rare GU tumors. **Methods:** E-VIRTUE is an open-label, non-randomized, Phase 2 multicenter study. Eligible patients must have locally advanced or metastatic urinary tract pure adenocarcinoma, urinary tract pure SCC or refractory GCTs and have measurable disease by RECIST 1.1. Patients may have received any number of lines of prior systemic therapy except EV or other MMAE-based ADCs, and GCT patients must be refractory to all curative SOC treatments. Each histology will have an ICB-naïve and post anti-PD-1/PD-L1 ICB cohort: ICB-naïve patients will be given EV 1.25 mg/kg (maximum 125 mg) on Days 1 and 8 and pembrolizumab 200 mg on Day 1 of 21-day cycles, and post ICB patients will be given EV 1.25 mg/kg (maximum 125 mg) on Days 1, 8 and 15 of 28-day cycles. EV will be given for up to 5 years and pembrolizumab will be given for up to 2 years, or until progressive disease (PD) or unacceptable toxicity. Patients who stop pembrolizumab after achieving a complete response may resume it for 1 year after developing PD. The primary objective is to evaluate the objective response rate (ORR) in all cohorts. Secondary objectives include safety, progression-free survival (PFS) and overall survival (OS). The initial 6 cohorts will each be evaluated with exploratory intent. With 10 patients in each cohort, an exact binomial test with a 10% one-sided significance level will have 85.3% power to detect the difference between a very low (5%) ORR and a higher (30%) ORR. If there are $\geq$2/10 objective responses in any cohort, activity will be demonstrated. Additional histologies may be added after nectin-4 data emerges to justify their inclusion. Exploratory objectives include estimating the level of nectin-4 expression for each histology, performing DNA and RNA sequencing of tumor and blood samples, and observing changes in levels of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) with treatment and disease status. Clinical trial registration NCT06041503. Clinical trial information: NCT06041503. Research Sponsor: Astellas Pharma & Seagen Inc.; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4629 **Poster Session**

A phase II study of lurbinectedin with or without avelumab in small cell carcinoma of the bladder (LASER).

Nicholas I. Simon, Elias Chandran, Scot Anthony Niglio, Andre Rashad Kydd, Saad Omar Atiq, Lisa Ley, Tzu-fang Wang, Salah Boudjadi, Elizabeth Smith, Dilara Akbulut, Seth M. Steinberg, Andrea B Apolo; Genitourinary Malignancies Branch, CCR, NCI, NIH, Bethesda, MD; Perlmutter Cancer Center, NYU Langone Health, New York, NY; National Cancer Institute, Bethesda, MD; Laboratory of Pathology, CCR, NCI, NIH, Bethesda, MD; Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Small cell carcinoma of the bladder (SCCB) is a rare, aggressive malignancy accounting for <1% of all bladder malignancies. Given its rarity, few prospective randomized trials have been completed in SCCB. Most therapeutic evidence comes from retrospective case series and due to its histologic similarity to small cell lung cancer (SCLC), current guidelines recommend bladder cancers with any component of small cell histology be treated similarly to SCLC. Lurbinectedin is a novel alkylating agent which recently received accelerated approval from the FDA as a second line treatment for SCLC after demonstrating an overall response rate (ORR) of 35.2% and median duration of response (DoR) of 5.3 months (Trigo et al., Lancet Oncol, 2020). Avelumab is an anti-PD-L1 antibody FDA approved as maintenance treatment for patients with locally advanced or metastatic urothelial cancer (UC) without progression on frontline chemotherapy. Case reports have demonstrated that second line options in SCLC, including immunotherapy, appear to have some efficacy in SCCB. The purpose of this study is to assess the efficacy of lurbinectedin, either alone or in combination with avelumab, in participants with SCCB or other high grade neuroendocrine tumors (HGNETs) of the urinary tract. **Methods:** LASER (NCT06228066) is a phase II, multisite, open label, nonrandomized study with two cohorts. Eligible patients must have pathologically confirmed SCCB or other HGNETs of the urinary tract. Patients with mixed histologies, with any component of neuroendocrine tumor, are eligible. Patients must have received or be ineligible/refused frontline platinum/etoposide therapy. Participants in Cohort 1 must have received prior immune checkpoint inhibitors (ICIs) or be ineligible for treatment with ICI. These patients will receive lurbinectedin 3.2mg/m2 IV every 21 days. Participants in Cohort 2 must be ICI naïve but eligible to receive them. These patients will receive lurbinectedin 3.2mg/m2 IV and avelumab 800mg IV every 21 days. The primary endpoint for both cohorts is ORR, with key secondary endpoints including clinical benefit rate, PFS, OS, and DoR. The study will be conducted using a Simon minimax two stage design to rule out an ORR of 5% in favor of an ORR of 25% or greater in each cohort. If 1 of the first 12 patients has a response accrual will continue up to 16 evaluable patients per cohort. Accrual ceiling will be set at 35 patients. Exploratory objectives include analyzing peripheral immune subsets, DNA and RNA sequencing of tumors, and measurement of ctDNA and CTCs. Clinical trial information: NCT06228066. Research Sponsor: Jazz Pharmaceuticals; EMD Serono.

TPS4630 Poster Session

Safety and immunological effects of ablative radiotherapy followed by pembrolizumab in patients with advanced adrenocortical carcinoma.

Nitya Prabhakar Raj, Christopher H. Crane, Etay Ziv, Anuradha Gopalan, Joanne F. Chou, Marinela Capanu, Diane Lauren Reidy, Carla Hajj; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Adrenocortical carcinoma (ACC) is a rare and aggressive cancer with poor prognosis. While pembrolizumab is a NCCN recommended treatment, our prior study showed no benefit in patients with liver metastases (NCT02673333).[1] Preclinical evidence suggests combining liver-directed radiation therapy (RT) with pembrolizumab might enhance anti-tumor immunity.[2] Our current study will assess the safety and describe preliminary efficacy data for ablative RT to symptomatic liver metastases followed by treatment with pembrolizumab in patients with advanced ACC. **Methods:** This is a single-center pilot study. Main inclusion criteria include: adult patients with metastatic ACC with symptomatic liver metastases, presence of extrahepatic metastases, ECOG 0-1. Ablative RT in 5 or 10 once daily fractions will be delivered over 1 to 2 weeks; pembrolizumab treatment (200mg Q3W) will begin one week after RT completion. The primary objective is to evaluate the safety of treatment with ablative RT followed by pembrolizumab. The study will include a 6 patient safety lead-in, with 10 to 12 patients enrolled in total. The secondary endpoint, efficacy, is defined as the objective response (partial and complete response) according to RECIST v1.1, in the hepatic and extrahepatic disease. Correlative objectives include evaluation of the innate and adaptive immune response during treatment through analysis of pre- and on-treatment blood and tumor tissue samples, circulating tumor (ct) DNA analyses, and PD-L1 and next-generation sequencing testing in pre-treatment tumor tissue samples to evaluate for biomarkers of response and resistance. This trial began enrollment in 9/27/2023, with 3 patients enrolled to date. References: [1]Raj N, Zheng Y, Kelly V, Katz SS, Chou J, Do RKG, et al. PD-1 Blockade in Advanced Adrenocortical Carcinoma. J Clin Oncol. 2020;38(1):71-80. [2]Yu J, Green MD, Li S, Sun Y, Journey SN, Choi JE, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med. 2021;27(1):152-64. Clinical trial information: NCT06066333. Research Sponsor: Drew O'Donoghue Fund.