Nivolumab plus ipilimumab (NIVO+IPI) vs gemcitabine-carboplatin (gem-carbo) chemotherapy for previously untreated unresectable or metastatic urothelial carcinoma (mUC): Final results for cisplatin-ineligible patients from the CheckMate 901 trial.

Michiel Simon Van Der Heijden, Matthew D. Galsky, Thomas Powles, Andrea Necchi, Dingwei Ye, Peng Zhang, Aristotelis Bamias, Pablo Maroto-Rey, Michel Pavic, Jens Bedke, Ja Hyeon Ku, Mauricio Burotto, Gwenaelle Gravis, Jan Oldenburg, Yoshihiko Tomita, Yüksel Ürün, Jeiry Filian, Anlong Li, Emmanouil Spanakis, Guru P. Sonpavde; Netherlands Cancer Institute, Amsterdam, Netherlands; Icahn School of Medicine at Mount Sinai, New York, NY; Barts Cancer Centre, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, London, United Kingdom; Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Fudan University Cancer Hospital, Xuhui, Shanghai, China; Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; National and Kapodistrian University of Athens, Athens, Greece; Department of Medical Oncology, Hospital Sant Pau, Barcelona, Spain; Centre Hospitalier Universitaire de Sherbrooke (CRCHUS), Sherbrooke, QC, Canada; Eberhard Karls University of Tübingen, Tübingen, Germany; Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; Bradford Hill Clinical Research Center, Santiago, Chile; Institut Paoli-Calmettes, Aix-Marseille Universite, CRCM, Marseille, France; Akershus University Hospital (Ahus), Lørenskog, Norway; Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Ankara University, Ankara, Turkey; Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Boudry, Neuchâtel, Switzerland; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Platinum-based chemotherapy is a standard of care (SOC) for unresectable or mUC; patients (pts) ineligible for cisplatin (cis) have worse outcomes. The phase 3, global, open-label, randomized CheckMate 901 trial (NCT03036098) compared NIVO+IPI vs gem-carbo in cis-ineligible pts with previously untreated unresectable or mUC. Here, we report final results. **Methods:** Pts with previously untreated, histologically confirmed, unresectable or mUC who were cis-ineligible (glomerular filtration rate $\geq$ 30 to $<$ 60 mL/min) were randomized 1:1 to NIVO 1 mg/kg + IPI 3 mg/kg Q3W up to 4 cycles, then NIVO 480 mg Q4W until disease progression/unacceptable toxicity or up to 2 years, or to gem-carbo Q3W for up to 6 cycles. Pts were stratified by tumor PD-L1 expression and liver metastasis. The primary endpoint was overall survival (OS). Progression-free survival (PFS) by blinded independent central review (BICR) was a secondary endpoint. Objective response rate (ORR) per BICR, duration of response (DOR) per BICR, and safety were exploratory. **Results:** 445 pts were randomized (NIVO+IPI, n = 221; gem-carbo, n = 224). Median time to treatment discontinuation (95% CI) was 2.2 (2.1–3.5) mo with NIVO+IPI vs 3.8 (3.5–3.9) mo with gem-carbo. After minimum follow-up (58.3 mo), the primary endpoint of OS did not meet the threshold for significance (median, 19.1 mo with NIVO+IPI vs 13.2 mo with gem-carbo; HR 0.79 [98.27% CI, 0.61–1.01]; P = 0.0245; Table). PFS, ORR, and DOR are shown in the Table. Any-grade treatment-related adverse events (TRAEs) occurred in 89.0% (grade 3–4, 47.2%) of NIVO+IPI-treated and 92.9% (grade 3–4, 76.3%) of gem-carbo-treated pts; any-grade TRAEs leading to discontinuation occurred in 31.2% and 14.2% of pts, respectively. There were 8 deaths related to toxicity (NIVO+IPI, 7; gem-carbo, 1). **Conclusions:** NIVO+IPI did not meet the threshold of statistical significance for improved OS vs gem-carbo in cis-ineligible pts with untreated unresectable or mUC. Durable response and favorable landmark OS with NIVO+IPI show meaningful activity from a chemotherapy-free regimen of finite duration. No new safety signals were identified. Clinical trial information: NCT03036098. Research Sponsor: Bristol Myers Squibb.

Efficacy (95% CI)	NIVO+IPI; n = 221	Gem-carbo; n = 224	HR
mOS	19.1 (13.5–22.6)	13.2 (11.6–15.2)	0.79 (98.27% CI, 0.61–1.01)[a]; P = 0.0245[b]
12-mo OS rate	59.7 (52.8–65.9)	54.3 (47.4–60.7)	–
36-mo OS rate	29.6 (23.5–35.9)	19.3 (14.3–24.9)	–
mPFS	5.3 (3.8–6.0)	5.9 (5.6–7.6)	0.90 (95% CI, 0.72–1.12)
12-mo PFS rate	31.5 (25.0–38.2)	17.2 (11.8–23.4)	–
36-mo PFS rate	20.0 (14.3–26.5)	4.9 (2.1–9.6)	–
ORR	35.3 (29.0–42.0)	38.8 (32.4–45.6)	-
mDOR	25.0 (14.8–61.8); n = 78	7.4 (5.8–8.5); n = 87	-

[a]Statistical inference based on adjusted CI: 95% CI, 0.64–0.97.
[b]mOS did not reach the prespecified threshold of statistical significance of P = 0.0173.
m, median.

Avelumab + sacituzumab govitecan (SG) vs avelumab monotherapy as first-line (1L) maintenance treatment in patients (pts) with advanced urothelial carcinoma (aUC): Interim analysis from the JAVELIN Bladder Medley phase 2 trial.

Jeannie Hoffman-Censits, Marinos Tsiatas, Peter Chang, Miso Kim, Lorenzo Antonuzzo, Sang Joon Joon Shin, Georgios Gakis, Normand Blais, Se Hyun Kim, Annabel Smith, Jose Angel Arranz Arija, Harvey Yu-Li Su, Flora Zagouri, Marco Maruzzo, Christophe Tournigand, Frederic Forget, Astrid Schneider, Karin Tyroller, Natalia Jacob, Begoña P. Valderrama; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD; Department of Medical Oncology, Athens Medical Center, Marousi, Greece; Taipei Veterans General Hospital, and Institute of Biopharmaceutical Science, National Yang Ming Chiao Tung University, Hsinchu, Taiwan; Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; Clinical Oncology Unit, Careggi University Hospital, Florence, Italy, and Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; University Clinic and Polyclinic of Urology, Martin-Luther-University of Halle-Wittenberg, Halle, Germany; Hematology-Oncology Division, University of Montreal Health Centre (CHUM), Montréal, QC, Canada; Division of Hematology-Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; Icon Cancer Centre, Adelaide, Australia; Department of Medical Oncology, Hospital Universitario Gregorio Marañón, Madrid, Spain; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; Department of Clinical Therapeutics, Alexandra Hospital National and Kapodistrian University of Athens, Athens, Greece; IOV—Istituto Oncologico Veneto IRCCS, Padova, Italy; Department of Medical Oncology, Hôpital Henri Mondor, AP-HP, UPEC, Créteil, France; Centre Hospitalier de l'Ardenne, Libramont-Chevigny, Belgium; The Healthcare Business of Merck KGaA, Darmstadt, Germany; EMD Serono, Billerica, MA; Hospital Universitario Virgen del Rocío, Seville, Spain

Background: In the JAVELIN Bladder 100 phase 3 trial, avelumab 1L maintenance + best supportive care (BSC) significantly prolonged overall survival (OS) and progression-free survival (PFS) vs BSC alone in pts with aUC without progression following 1L platinum-based chemotherapy (PBC). The JAVELIN Bladder Medley phase 2 trial is investigating the combination of avelumab with other antitumor agents in this pt population to assess efficacy and safety vs avelumab maintenance monotherapy. SG is a Trop-2–directed antibody and topoisomerase inhibitor drug conjugate being investigated in solid tumors. Here we report an interim analysis of avelumab + SG vs avelumab monotherapy. **Methods:** Eligible pts had unresectable locally advanced or metastatic UC, ECOG performance status (PS) 0-1, and no disease progression after 4-6 cycles of 1L PBC. Pts were randomized 2:1 to avelumab + SG or avelumab monotherapy, stratified by presence of visceral metastases at start of 1L PBC. Primary endpoints were investigator-assessed PFS and safety; OS was a secondary endpoint. For PFS and OS analyses, data in the avelumab monotherapy arm were extended per protocol using propensity score-weighted JAVELIN Bladder 100 data. **Results:** At data cutoff (Sep 16, 2024), 38 of 74 pts (51.4%) in the avelumab + SG arm and 10 of 37 pts (27.0%) in the avelumab monotherapy arm were still receiving study treatment. In the avelumab + SG and avelumab monotherapy arms, respectively, median age was 70 and 67 years, 50.0% and 51.4% had visceral metastases at start of 1L PBC, and a lower proportion of pts in the avelumab + SG arm had ECOG PS of 1 (31.1% vs 54.1%). Median PFS was 11.17 months (95% CI, 7.43-not estimable [NE]) with avelumab + SG vs 3.75 months (95% CI, 3.32-6.77) with avelumab monotherapy (hazard ratio [HR], 0.49 [95% CI, 0.31-0.76]). OS data were immature at cutoff; median OS was not reached (95% CI, 15.51-NE) in the avelumab + SG arm vs 23.75 months (95% CI, 18.79-30.82) in the avelumab monotherapy arm (HR, 0.79 [95% CI, 0.42-1.50]). In the avelumab + SG and avelumab monotherapy arms, respectively, treatment-related adverse events (TRAEs) of any grade occurred in 71 (97.3%) vs 23 pts (63.9%), and were grade ≥3 in 51 (69.9%) vs 0 pts. TRAEs led to discontinuation of both avelumab + SG in 4.1% (SG only in 12.3%) vs avelumab monotherapy in 2.8%. One pt in the avelumab + SG arm had a SG-related AE that led to death (acute subarachnoid hemorrhage in the setting of sepsis and pancytopenia). **Conclusions:** In pts with aUC without progression after 1L PBC, avelumab + SG as maintenance treatment improved PFS vs avelumab monotherapy. TRAEs were more frequent in the combination arm and were consistent with the known safety profile of SG and avelumab. Further investigation of avelumab in combination with anti–Trop-2 antibody-drug conjugates in aUC is warranted. Clinical trial information: NCT05327530. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Exploratory analysis of responders from the phase 3 EV-302 trial of enfortumab vedotin plus pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC).

Shilpa Gupta, Jens Bedke, Michiel Simon Van Der Heijden, Begoña P. Valderrama, Eiji Kikuchi, Jeannie Hoffman-Censits, Gopa Iyer, Christof Vulsteke, Steffen Rausch, Se Hoon Park, Alexandra Drakaki, Waddah Arafat, Umang Swami, Ignacio Duran, Jian-Ri Li, Blanca Homet Moreno, Seema Rao Gorla, Xuesong Yu, Yi-Tsung Lu, Thomas Powles; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Department of Urology & Eva Mayr-Stihl Cancer Center, Stuttgart, Germany; Netherlands Cancer Institute, Amsterdam, Netherlands; Hospital Universitario Virgen del Rocío, Seville, Spain; St. Marianna University School of Medicine, Kawasaki, Japan; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Center, Baltimore, MD; Memorial Sloan Kettering Cancer Center, New York, NY; Integrated Cancer Center Ghent, AZ Maria Middelares and Center for Oncological Research (CORE), Antwerp University, Antwerp, Belgium; Eberhard Karls University, Tübingen, Germany; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; University of California, Los Angeles Medical Center, Los Angeles, CA; Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Hospital Universitario Marqués de Valdecilla, IDIVAL Santander, Santander, Spain; Taichung Veterans General Hospital, Taichung, Taiwan; Merck & Co., Inc., Rahway, NJ; Astellas Pharma, Inc., Northbrook, IL; Pfizer Inc., Bothell, WA; Barts Cancer Centre, Queen Mary University of London, London, United Kingdom

Background: EV-302/KEYNOTE-A39 (NCT04223856) showed significant PFS and OS benefits for pts with previously untreated la/mUC treated with EV+P vs chemo, which established EV+P as the SOC in this population. This exploratory analysis presents efficacy and safety results for responders, focusing on pts with confirmed complete response (cCR). **Methods:** Pts were randomized 1:1 to receive EV (1.25 mg/kg; Days 1 and 8; IV) + P (200 mg; Day 1; IV) or chemo (gemcitabine + cisplatin/carboplatin); all Q3W. Primary endpoints were PFS by BICR and OS. Secondary endpoints included ORR, DOR, and safety. An exploratory analysis evaluated outcomes in pts with cCR. A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Median follow-up (data cutoff: Aug 8, 2024) was 29.1 mo (95% CI, 28.5-29.9). 886 pts were randomized to EV+P (n = 442) vs chemo (n = 444). Confirmed ORR (CR+PR) was 67.5% with EV+P and 44.2% with chemo; cCR was 30.4% and 14.5%, respectively. Baseline characteristics of responders were generally consistent with the ITT population. Among pts with cCR in the EV+P arm, 38 (28.6%) had upper tract disease and 20 (15%) had liver metastases. For pts with cCR, mPFS by BICR was not reached (NR) with EV+P and 26.9 mo with chemo (HR, 0.36; 95% CI, 0.21-0.61); mOS was NR with both EV+P and chemo (HR, 0.37; 95% CI, 0.17-0.80). Median duration of CR was NR for EV+P and 15.2 mo for chemo. Efficacy data are in the Table. Among pts with cCR in the EV+P arm, the median number of cycles was 13 (range, 1-50) for EV and 27 (range, 1-35) for P; median treatment (tx) duration was 22.0 mo (range, 0.7-35.4). Safety among responders was generally consistent with previous reports. TRAEs leading to dose modification in pts with cCR are in the Table. Grade ≥3 TRAEs occurred in 61.7% and 71.9% of pts with cCR in the EV+P and chemo arms, respectively. EV tx-related AESIs and P tx-emergent AEOSI profiles were generally consistent with previous reports. There were no tx-related deaths among pts with cCR. **Conclusions:** In the EV+P arm, the proportion of pts achieving cCR was twice that in the chemo arm. Consistent with the ITT data, EV+P reduced the risk of progression or death vs chemo in pts achieving cCR, with appropriate dose modifications. These data reinforce EV+P as the SOC for 1L tx of pts with la/mUC. Clinical trial information: NCT04223856. Research Sponsor: The EV-302 study was funded by Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	EV+P cCR: n=133	Chemo cCR: n=64
Median PFS, mo (95% CI)	NR (NE-NE)	26.9 (16.6-NE)
24-mo PFS rate, % (95% CI)	78.2 (69.8-84.6)	53.7 (40.0-65.5)
Median OS, mo (95% CI)	NR (39.3-NE)	NR (32.1-NE)
24-mo OS rate, % (95% CI)	95.4 (90.0-97.9)	85.8 (74.6-92.4)
Median DOCR, mo (95% CI)	NR (NE-NE)	15.2 (10.3-NE)
24-mo cCR rate, % (95% CI)	74.3 (65.1-81.4)	43.2 (28.7-56.9)
TRAEs leading to dose modification (n, %)		
Dose interruption of EV	94 (70.7)	-
Dose reduction of EV	86 (64.7)	-
Dose interruption of P	86 (64.7)	-

Circulating tumor DNA (ctDNA) in patients with muscle-invasive bladder cancer (MIBC) who received perioperative durvalumab (D) in NIAGARA.

Thomas Powles, Michiel Simon Van Der Heijden, Ying Wang, James W.F. Catto, Joshua J. Meeks, Hikmat Al-Ahmadie, Hiroyuki Nishiyama, Agrin Moeini Mortazavi, Toan Quang Vu, Lorenzo Antonuzzo, Tae-Hwan Kim, Vagif Atduev, Hiroaki Kikukawa, Bernhard J. Eigl, Yousef Zakharia, Kazuo Nishimura, Svetlana Ho, Wenjing Xin, Yashaswi Shrestha, Matthew D. Galsky; Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, United Kingdom; Netherlands Cancer Institute, Amsterdam, Netherlands; AstraZeneca, Waltham, MA; Division of Clinical Medicine, University of Sheffield, Sheffield, United Kingdom; Northwestern University Feinberg School of Medicine, Chicago, IL; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Urology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan; AstraZeneca, Barcelona, Spain; Department of Internal Medicine 3, Vietnam National Cancer Hospital, Ha Noi, Viet Nam; Department of Experimental and Clinical Medicine, University of Florence. Oncology Unit, Careggi University Hospital, Florence, Italy; Department of Urology, Kyungpook National University School of Medicine, Daegu, South Korea; Volga District Medical Center, Federal Medical-Biological Agency, Nizhny Novgorod, Russian Federation; Department of Urology, National Hospital Organisation Kumamoto Medical Center, Kumamoto, Japan; British Columbia Cancer Agency, Vancouver, BC, Canada; University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA; Department of Urology, Osaka International Cancer Institute, Osaka, Japan; AstraZeneca, Gaithersburg, MD; AstraZeneca, Gothenburg, Sweden; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Department of Medical Oncology, New York, NY

Background: In the phase 3 NIAGARA trial (NCT03732677) of patients (pts) with cisplatin-eligible MIBC, addition of perioperative D to neoadjuvant chemotherapy (NAC) demonstrated a statistically significant and clinically meaningful improvement in event-free survival (EFS) and overall survival compared with NAC alone, and a 10% higher pathological complete response (pCR) rate, with a manageable safety profile and no impact on the feasibility of surgery. Here, we report a planned exploratory analysis of ctDNA and association with clinical outcomes from NIAGARA. **Methods:** NIAGARA enrolled cisplatin-eligible pts with MIBC (cT2-T4aN0/1M0) planned for radical cystectomy (RC). Pts were randomized 1:1 to receive either neoadjuvant D (1500 mg IV Q3W) and NAC (cisplatin + gemcitabine IV Q3W) for 4 cycles followed by RC, then adjuvant D monotherapy (1500 mg IV Q4W) for 8 cycles (D arm), or NAC followed by RC alone (comparator [C] arm). Dual primary endpoints were pCR and EFS. Disease-free survival (DFS) was a secondary endpoint. Plasma ctDNA was assessed using the Signatera personalized, tumor-informed molecular residual disease (MRD) assay (Natera, Inc, Austin, TX, USA). ctDNA was assessed at baseline (screening or neoadjuvant C1D1, n = 460), after neoadjuvant treatment prior to RC (pre-RC, n = 422), and at C1D1 of the adjuvant phase (post-RC, n = 345). **Results:** Of 1063 randomized pts, 462 comprised the biomarker-evaluable population (237 D arm; 225 C arm). Patient characteristics were similar to the ITT population. Overall, the ctDNA+ rate at baseline was 57% (260/460) and decreased to 22% (94/422) after neoadjuvant treatment at pre-RC. ctDNA clearance rates from baseline to pre-RC were 41% in the D arm and 31% in the C arm. The non-pCR rate was 97% (86/89) among pts with pre-RC ctDNA+ status. Overall ctDNA+ rate post-RC was 9% (31/345). EFS benefit in the D arm vs the C arm was observed in both the baseline ctDNA+ and ctDNA− groups (Table). DFS benefit with perioperative D was observed in post-RC ctDNA+ and ctDNA− groups (Table). **Conclusions:** In this exploratory analysis, ctDNA+ status at pre-RC was associated with non-pCR. Higher ctDNA clearance from baseline to pre-RC in the D arm indicated the additional benefit of D plus NAC vs NAC alone. Perioperative D provided an EFS benefit to both pts with ctDNA+ and ctDNA− status at baseline; a similar trend was observed with DFS based on ctDNA status post-RC. These results further support the perioperative D regimen for pts with MIBC. Funding: AstraZeneca. Clinical trial information: NCT03732677. Research Sponsor: AstraZeneca.

	EFS				DFS			
	Baseline ctDNA+		Baseline ctDNA-		Post-RC ctDNA+		Post-RC ctDNA-	
	D	C	D	C	D	C	D	C
n	137	123	99	101	9	8	129	126
Median (95% CI), months	NR (NR–NR)	32.3 (24.3–NR)	NR (NR–NR)	NR (NR–NR)	9.5 (2.8–NR)	6.2 (2.9–NR)	NR (NR–NR)	NR (NR–NR)
Hazard ratio (95% CI)	0.73 (0.51–1.06)		0.45 (0.25–0.84)		NC*		0.49 (0.28–0.84)	

CI, confidence interval; NC, not calculable; NR, not reached.
*NC due to <20 events between arms.

LBA4504 **Oral Abstract Session**

Mitomycin plus BCG as adjuvant intravesical therapy for high-risk, non–muscle-invasive bladder cancer: A randomized phase 3 trial (ANZUP 1301).

Dickon Hayne, Alison Yan Zhang, Hayley Thomas, Stephen P. McCombie, Cynthia Hawks, Paul Anderson, Patricia A. Bastick, Emma Kate Beardsley, William Green, Mark Frydenberg, Jeremy Grummet, Joseph Ischia, Laurence Krieger, Andrew Mitterdorfer, Manish Patel, Shomik Sengupta, Ratnesh Kumar Srivastav, Andrew David Redfern, Ian D. Davis, Martin R. Stockler, The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); UWA Medical School, University of Western Australia, Perth, Western Australia, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; UWA Medical School, University of Western Australia, Perth, Australia; Royal Melbourne Hospital, Department of Urology, Richmond, Australia; Southside Cancer Care, Kogarah, NSW, Australia; Frankston Hospital, Dept. of Medical Oncology, Melbourne, Australia; Nottingham University Hospitals, Dept. of Urology, Nottingham, United Kingdom; Monash University Faculty of Medicine, Clayton, Australia; Monash University, Melbourne, Australia; University of Melbourne, Austin Health , Heidelberg Vic, Australia; Genesis Care, North Shore, Sydney, NSW, Australia; Concord Repatriation General Hospital, Dept. of Urology, Sydney, Australia; University of Sydney, Sydney, Australia; Monash University Eastern Health Clinical School, Box Hill, Australia; The Tweed Hospital, Tweed Heads, NSW, Australia; Fiona Stanley Hospital, Murdoch, Western Australia, Australia; Eastern Health Clinical School, Monash University and Eastern Health, Melbourne, Australia; NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, NSW, Australia

Nivolumab plus ipilimumab vs sunitinib for first-line treatment of advanced renal cell carcinoma: Final analysis from the phase 3 CheckMate 214 trial.

Toni K. Choueiri, Bernard Escudier, David F. McDermott, Mauricio Burotto, Hans J. Hammers, Elizabeth R. Plimack, Camillo Porta, Saby George, Thomas Powles, Frede Donskov, Michael B. Atkins, Christian K. Kollmannsberger, Marc-Oliver Grimm, Yoshihiko Tomita, Brian I. Rini, Ruiyun Jiang, Maximiliano van Kooten Losio, Chung-Wei Lee, Robert J. Motzer, Nizar M. Tannir; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Gustave Roussy, Villejuif, France; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; Bradford Hill Clinical Research Center, Santiago, Chile; UT Southwestern Kidney Cancer Program, Dallas, TX; Fox Chase Cancer Center, Philadelphia, PA; University of Pavia, Pavia, Italy; Roswell Park Cancer Institute, Buffalo, NY; Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, United Kingdom; University Hospital, Aarhus and Southern Denmark University Hospital, Esbjerg, Aarhus, Denmark; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; British Columbia Cancer Agency, Vancouver, BC, Canada; Jena University Hospital, Jena, Germany; Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Vanderbilt University Medical Center, Nashville, TN; Bristol Myers Squibb, Princeton, NJ; Memorial Sloan Kettering Cancer Center, New York, NY; University of Texas MD Anderson Cancer Center, Houston, TX

Background: First-line nivolumab plus ipilimumab (NIVO+IPI) provided substantial long-term survival benefits over sunitinib (SUN) in patients (pts) with advanced renal cell carcinoma (aRCC) in the CheckMate 214 trial. We now report final efficacy and safety data in the intent-to-treat (ITT) population and by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk. **Methods:** Pts with clear cell aRCC were randomized 1:1 to NIVO 3 mg/kg + IPI 1 mg/kg Q3W×4 then NIVO (3 mg/kg or 240 mg Q2W or 480 mg Q4W); or SUN 50 mg once daily for 4 weeks on, 2 weeks off. Efficacy endpoints included overall survival (OS), and independent radiology review committee (IRRC)-assessed progression-free survival (PFS) and objective response rate (ORR) in intermediate/poor-risk (I/P; primary), ITT (secondary), and favorable-risk (FAV; exploratory) pts. Response was assessed using RECIST v1.1. **Results:** With 9 years median follow-up, OS was improved with NIVO+IPI vs SUN in ITT (HR 0.71) and I/P (HR 0.69) pts. The probability of OS at 108 months was 31% vs 20% in ITT pts and 30% vs 19% in I/P pts, respectively. In pts with FAV risk, the HR for OS improved from 1.45 at first report (Motzer *NEJM* 2018) to 0.80 at 9 years, showing a delayed benefit with NIVO+IPI vs SUN. OS probabilities at 108 months were 35% vs 22% in FAV pts, respectively (Table). The probability of PFS at 96 months with NIVO+IPI vs SUN was 23% vs 9% in ITT pts, 25% vs 9% in I/P pts, and 13% vs 11% in FAV pts. The probability of remaining in response through 96 months with NIVO+IPI vs SUN was 48% vs 19% in ITT pts, 50% vs 23% in I/P pts, and 36% vs not available (NA) in FAV pts. No new treatment-related deaths occurred in either arm. Additional subgroup analyses will be presented. **Conclusions:** In the longest and final phase 3 follow-up (9 years) of a first-line checkpoint inhibitor combination in aRCC, milestone rates of OS and PFS and durable response remained higher with NIVO+IPI vs SUN. No new safety signals emerged. NIVO+IPI remains a standard first-line option in aRCC. Clinical trial information: NCT02231749. Research Sponsor: Bristol Myers Squibb.

Arm; n	ITT NIVO+IPI; 550	SUN; 546	I/P NIVO+IPI; 425	SUN; 422	FAV NIVO+IPI; 125	SUN; 124
mOS (95% CI), mo	53 (46–64)	38 (32–44)	47 (35–56)	26 (22–33)	78 (65–92)	67 (56–80)
108-mo OS probabilities (95% CI), %	31 (27–35)	20 (16–23)	30 (26–35)	19 (15–23)	35 (27–44)	22 (15–30)
mPFS (95% CI), mo	12 (10–16)	12 (10–15)	12 (9–17)	9 (7–11)	13 (10–18)	29 (23–43)
96-mo[a] PFS probabilities (95% CI), %	23 (18–27)	9 (5–15)	25 (20–31)	9 (4–15)	13 (6–22)	11 (3–27)
ORR per IRRC (95% CI); CR, %	39 (35–44); 12	33 (29–37); 3	42 (38–47); 12	27 (23–32); 3	30 (22–38); 13	52 (43–61); 6
mDOR (95% CI), mo	76 (59–NE)	25 (20–33)	83 (54–NE)	20 (16–26)	61 (23–NE)	33 (25–51)
96-mo[a] DOR probabilities (95% CI), %	48 (39–55)	19 (10–31)	50 (41–58)	23 (13–36)	36 (17–56)	NA[b]

[a]96-mo probabilities reported due to small numbers of pts at risk at 108 mo.
[b]No pts remain at risk.
CR, complete response; DOR, duration of response; m, median; NE, not estimable.

4506 Oral Abstract Session

Combination casdatifan plus cabozantinib expansion cohort of phase 1 ARC-20 study in previously treated patients with clear cell renal cell carcinoma.

Toni K. Choueiri, Moshe C. Ornstein, Pedro C. Barata, Marc Ryan Matrana, Jaime R. Merchan, Craig Gedye, Clara Hwang, Rohit Kumar, Jae Lyun Lee, Yinghui Guan, Mohammad Ghasemi, Syed Quadri, Christopher Negro, Jianfen Chen, Paul G. Foster, Manish Monga, Bradley Alexander McGregor, Sun Young Rha, Alexandra Drakaki; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Cleveland Clinic, Cleveland, OH; University Hospitals Seidman Cancer Center, Cleveland, OH; Ochsner Health, New Orleans, LA; Department of Medical Oncology, University of Miami Leonard M. Miller School of Medicine, University of Miami, Miami, FL; ICON Cancer Center Adelaide, Kurralta Park, Australia; Henry Ford Cancer - Detroit, Detroit, MI; James Graham Brown Cancer Center, University of Louisville, Louisville, KY; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Arcus Biosciences, Hayward, CA; Dana-Farber Cancer Institute, Boston, MA; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; University of California, Los Angeles Medical Center, Los Angeles, CA

Background: Hypoxia-inducible factor 2-alpha (HIF-2α) is highly dysregulated in clear cell renal cell carcinoma (ccRCC), resulting in increased expression of proteins involved with angiogenesis, proliferation, and cancer cell survival. Casdatifan is an orally bioavailable small-molecule HIF-2α inhibitor. We investigated the safety and efficacy of casdatifan in combination with the anti–vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) cabozantinib in previously treated patients with ccRCC in an expansion cohort (casdatifan + cabozantinib) of the phase 1, open-label ARC-20 (NCT05536141) trial. **Methods:** Patients enrolled in the casdatifan + cabozantinib expansion cohort were previously treated with immunotherapy (IO) alone or with anti-VEGF therapies. Casdatifan 100 mg and cabozantinib 60 mg were given orally once daily. Endpoints included the incidence of treatment-emergent adverse events (AEs) and objective response rate (ORR) by RECIST v1.1. This study is ongoing; data as of January 3, 2025, are reported. **Results:** Overall, 27 patients with a median (range) follow-up of 2.9 (0.1–6.8) months were enrolled. At data cut off, prior treatment settings included adjuvant only (n = 5/26) and metastatic (1L n = 17/26; 2L n = 4/26). Prior therapies included IO only (n = 15/26) or IO plus VEGFR-TKI (n = 11/26). All grade AEs occurred in 89% of patients with the most common being anemia (n = 16 [59%]) and fatigue (n = 15 [56%]). Most common ($>10\%$) grade ≥ 3 AEs were anemia (n = 7 [26%]) and hypoxia (n = 3 [11%]). No cardiac events were reported. AEs leading to casdatifan-only, cabozantinib-only, or both casdatifan + cabozantinib dose reductions occurred in 3 (11%), 7 (26%), and 2 (7%) patients, respectively. Only one (4%) pt discontinued due to an AE, hypoxia related to casdatifan. Responses continue to be observed among the efficacy evaluable population (n = 22; as of January 27, 2025) with ORR of 41% (n = 1 complete response; n = 8 partial response). Activity was seen across all IMDC risk groups. **Conclusions:** In previously treated patients with ccRCC, casdatifan 100 mg in combination with cabozantinib 60 mg had a manageable AE profile with promising clinical activity. These data support continued evaluation of this combination in the phase 3 PEAK-1 clinical trial. Clinical trial information: NCT05536141. Research Sponsor: Arcus Biosciences, Inc.

Hypoxia-inducible factor-2α (HIF-2α) inhibitor belzutifan in von Hippel-Lindau (VHL) disease–associated neoplasms: 5-year follow-up of the phase 2 LITESPARK-004 study.

Vivek Narayan, Eric Jonasch, Othon Iliopoulos, Benjamin L. Maughan, Stephane Oudard, Tobias Else, Jodi Kathleen Maranchie, Ane Bundsbæk Bøndergaard Iversen, Katy Beckermann, Jerry Cornell, Rodolfo F. Perini, Yanfang Liu, W Marston Linehan, Ramaprasad Srinivasan; Hospital of the University of Pennsylvania, Philadelphia, PA; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Department of Medical Oncology, Hôpital Européen Georges Pompidou, Institut du Cancer Paris CARPEM, AP-HP.Centre – Université Paris Cité, Paris, France; Department of Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan, Ann Arbor, MI; University of Pittsburgh Medical Center, Pittsburgh, PA; Aarhus University Hospital, Aarhus, Denmark; Vanderbilt University, Nashville, TN; Merck & Co., Inc., Rahway, NJ; Merck and Co, Inc., Rahway, NJ; National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: The HIF-2α inhibitor belzutifan is approved for the treatment of patients with VHL disease–associated renal cell carcinoma (RCC), CNS hemangioblastomas (HB), or pancreatic neuroendocrine tumors (pNETs), not requiring immediate surgery based on previously reported results from the ongoing open-label phase 2 LITESPARK-004 study (NCT03401788). Updated results are presented after a minimum of 5 years of follow-up. **Methods:** Adults with germline *VHL* alterations, ≥1 measurable nonmetastatic RCC tumor, no tumor > 3 cm that required immediate surgery, no metastatic disease, no prior anticancer systemic treatment, and an ECOG PS of 0 or 1 received oral belzutifan 120 mg once daily until disease progression, unacceptable toxicity, or participant (pt) withdrawal. The primary end point was objective response rate (ORR) in VHL disease–associated RCC per RECIST v1.1 by independent review committee (IRC). Secondary end points included safety, ORR in non-RCC neoplasms, duration of response (DOR), and progression-free survival (PFS) per RECIST v1.1 by IRC. **Results:** Overall, 61 pts received ≥1 dose of belzutifan. Median study follow-up was 61.8 mo (range, 60.2-70.1). As of the April 1, 2024 data cutoff date, 35 pts (57%) remained on treatment. ORR was 70% for RCC, 50% for CNS HB, and 90% for pNETs. Additional efficacy results are in the Table. Among 14 pts (n = 18 eyes) with retinal HB, 100% (95% CI, 82-100) of eyes showed improvement per ophthalmologic assessment; median DOR for retinal HBs was not reached (NR; range, 8.5-61.0+ mo). At baseline, 59 of 61 pts (97%) had ≥1 prior VHL-related surgery. Within the 5 years before starting belzutifan, 46 of 61 pts (75%) had ≥1 surgery. Since starting belzutifan, 19 of 61 pts (31%) underwent VHL-related surgeries; 4 underwent surgery while on treatment and subsequently discontinued treatment, 8 underwent surgery after discontinuing treatment, and 7 are continuing treatment as of the data cutoff date. Grade 3 treatment-related adverse events (TRAEs) (most commonly anemia [n = 7; 11%]) were reported in 11 pts (18%). No grade 4 or 5 TRAEs occurred. Belzutifan was discontinued in 2 pts (3%) due to TRAEs (grade 1 dizziness and grade 2 intracranial hemorrhage). **Conclusions:** After 5 years of follow-up, belzutifan continues to demonstrate durable antitumor activity and a manageable safety profile, consistent with prior reports. Most pts remain on treatment after this period. Results continue to support the use of belzutifan in pts with VHL disease–related RCC, CNS HB, and pNETs who do not require immediate surgery. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; The Intramural Research Program of the National Institutes of Health, National Cancer Institute Center for Cancer Research, and a grant (UO1 CA236489) from the National Cancer Institute.

	RCC n = 61	CNS HB n = 50	pNETs n = 20
ORR, % (95% CI)	70 (57-82);7 CRs, 36 PRs	50 (36-64); 6 CRs; 19 PRs	90 (68-99); 13 CRs, 5 PRs
DOR, median (range), mo	NR (5.8+ to 60.8+)	60.3 (0.0+ to 60.3)	NR (11.0+ to 59.6+)
48-mo DOR rate	76%	82%	94%
PFS, median (95% CI), mo	NR (NR-NR)	63.5 (63.5-NR)	NR (NR-NR)
48-mo PFS rate	81%	79%	96%

ALLO-316 in advanced clear cell renal cell carcinoma (ccRCC): Updated results from the phase 1 TRAVERSE study.

Samer Ali Srour, Jad Chahoud, Alexandra Drakaki, Brendan D. Curti, Geoffrey Thomas Gibney, Sumanta Kumar Pal, Lily Tang, Sara Charmsaz, Joy Atwell, Paul B. Robbins, Chelsea Williams, Sri Ghatta, Chris Severyn, John Le Gall, Nizar M. Tannir, Ritesh R Kotecha; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Moffitt Cancer Center, Tampa, FL; UCLA Health, Los Angeles, CA; Providence Cancer Institute, Franz Clinic, Portland, OR; Georgetown University Hospital, Washington, DC; City of Hope Comprehensive Cancer Center, Duarte, CA; Allogene Therapeutics, San Francisco, CA; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Treatment options are limited for ccRCC after disease progression on immune checkpoint inhibitors (ICIs) and vascular endothelial growth factor (VEGF) inhibitors. CD70 is highly expressed on ccRCC. ALLO-316 is an investigational, healthy donor–derived allogeneic CD70 CAR T-cell product designed to recognize and kill both CD70 positive tumor cells and CD70 positive host T cells that drive allorejection. Initial data from the multicenter, phase 1a/b TRAVERSE study (NCT04696731) showed that ALLO-316 had manageable safety and promising antitumor activity. Updated results are presented. **Methods:** Patients were aged ≥18 years, had advanced ccRCC, ECOG PS of 0 or 1, and disease progression after ICI and VEGF-targeted therapy. After lymphodepletion (LD) with fludarabine and cyclophosphamide ± ALLO-647 (anti-CD52), patients received a single infusion of ALLO-316 following a 3+3 design (40-240 × 10^6 allogeneic CAR+ T cells). Primary end points were incidence of dose-limiting toxicities and adverse events. Objective response rate (ORR) was a secondary end point. **Results:** Of 44 patients who underwent LD, 39 received ALLO-316, and 38 were evaluable for disease outcome. Median age was 60 years, median of 3 prior therapies (range, 1-8), and 36 (82%) had CD70 positive ccRCC. As of January 2, 2025, median follow-up was 6.8 months (range, 0.8-39.5). Dose-limiting toxicities occurred in 2 patients (autoimmune hepatitis and cardiogenic shock in the setting of multiorgan failure). Treatment-emergent adverse events occurred in 42 patients (96%; grade ≥3, 37 patients [84%]). Grade ≥3 CRS occurred in 1 patient (2%; any grade, 25 patients [57%]), grade ≥3 ICANS in 0 patients (any grade, 4 patients [9%]), and grade ≥3 IEC-HS in 1 patient (2%; any grade, 8 patients [18%]). No GvHD occurred. As previously reported, 3 grade 5 adverse events were related to ALLO-316 (cardiogenic shock, failure to thrive, and sepsis). ORR for all LD regimens was 20% (6/30) overall for patients with CD70 positive tumors (Table). Confirmed ORR was 33% (3/9) for patients with CD70 ≥50% treated with the phase 1b regimen; all confirmed responses were ongoing (2.1, 6.7, and 8.4 months at the data cut-off). **Conclusions:** After a median follow-up of 6.8 months, a single infusion of ALLO-316 had manageable safety and encouraging antitumor activity in heavily pretreated patients. Further evaluation of ALLO-316 in CD70 positive ccRCC is warranted. Clinical trial information: NCT04696731. Research Sponsor: The anti-CD70 AlloCAR T program utilizes Cellectis technology and is licensed exclusively from Cellectis. Allogene holds global development and commercial rights. This research was in part made possible by an award from the CIRM (CLIN2-15343).; California Institute for Regenerative Medicine; Award Number CLIN2-15343.

	All CD70 positive n = 30	CD70 positive receiving phase 1b regimen[a] n = 12	CD70 negative or unknown n = 8
Best overall response (CR or PR at any visit), n/N (%)	8/30 (27)	4/12 (33)	0/8 (0)
CD70 ≥50[b]	8/24 (33)	4/9 (44)	–
CD70 <50[b]	0/6 (0)	0/3 (0)	–
ORR (confirmed CR or PR), n/N (%)	6/30 (20)	3/12 (25)	0/8 (0)
CD70 ≥50[b]	6/24 (25)	3/9 (33)	–
CD70 <50[b]	0/6 (0)	0/3 (0)	–

[a]ALLO-316 80 × 10^6 CAR+ T cells and LD with fludarabine 30 mg/m^2 + cyclophosphamide 500 mg/m^2.
[b]IHC-based tumor proportion score.

4509 Clinical Science Symposium

Exploratory analysis from NEOAVAX, a neoadjuvant trial of avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy.

Axel Bex, Johannes Cornelis van der Mijn, Niels Graafland, Johannes V. van Thienen, Sofie Wilgenhof, Brunolf Lagerveld, Patricia Zondervan, Reindert Jeroen A. Van Moorselaar, Mark Kockx, Pieter-Jan Van Dam, Pieter Mestdagh, Bernadett Emma Szabados, Christian U. Blank, Thomas Powles, John Haanen; Netherlands Cancer Institute, Amsterdam, The Netherlands, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Netherlands Cancer Insitute, Amsterdam, Netherlands; Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Onze Lieve, Vrouwe Gasthuis, Amsterdam, Netherlands; Amsterdam University Medical Center, Amsterdam, Netherlands; Amsterdam UMC, location VUMC, Amsterdam, Netherlands; CellCarta, Antwerp, Belgium; CellCarta, Wilrijk, Belgium; Barts Cancer Centre, London, United Kingdom; The Netherlands Cancer Institute, Amsterdam, Netherlands; Barts Cancer Centre, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, London, United Kingdom

Background: NEOAVAX (NCT03341845) is an open label, single arm, phase II trial, investigating 12 weeks of neoadjuvant avelumab/axitinib prior to nephrectomy in 40 pts with high-risk non-metastatic clear-cell (cc) RCC (cT1b-4 cN0-1 M0, Grades 3-4). Dynamic on-treatment increase of CD8+ tumor infiltrating lymphocytes (TILs) in the tumour microenvironment (TME) and the primary endpoint (radiographic partial response rate (RECIST 1.1) in the primary tumour (PT) in ≥25%) were reported previously together with safety and tolerability [1]. **Methods:** Exploratory analysis included pathologic response in the PT according to the International Neoadjuvant Melanoma Consortium (INMC) and multiplex immune histochemistry (IHC) of the TME including CD8+, CD8-granzyme-B+, CD8+CD39+, Foxp3+ cells and MHC-I in paired samples (pre-treatment biopsy and nephrectomy) from 40 pts;. IHC data were compared to RECIST 1.1 and pathologic response in the PT, and recurrence; Visium spatial transcriptomics was performed on 18 PT from pts with diverging clinical outcome. **Results:** The majority of pts (n=25 (62.5%) had no pathologic response (pNR) by INMC criteria. Twelve patients (30%) had a partial (pPR) and 3 (7.5%) a major pathological response (MPR). There was no association between pathological and radiographic response of the PT. Recurrence occurred in 1 of 3 pts (33%) with MPR at 36 mo, in 7 of 12 (58%) with a pPR at a median of 12 mo and in 14 of 25 (56%) with pNR at a median of 3 mo. Of 25 pts with pNR 7 died of disease (DoD; 28%). On IHC, intratumoural CD8+CD39+ on post-treatment PT samples was significantly associated with recurrence ($p<0.0001$). MPR associated with spatial co-localisation of tumour cells with tissue-resident macrophages, CD8+ cytotoxic T-cells, memory T-cells and B-cells. Gene Set Enrichment Analysis (GSEA) results for Reactome pathways in each Visium tumor spot cluster demonstrated intratumoural heterogeneity in post-treatment PT in select patients. **Conclusions:** Pathologic response and IHC post-treatment influx of CD8+CD39+ TILs associates with prolonged disease-free survival following neoadjuvant avelumab/axitinib. Particularly, pts with MPR had distinct spatial co-localisation gene signatures of tumour and immune cells in the TME. Despite 3 months of treatment, 62.5% of pts had no pathologic responses (defined by INMC as >50% vital tumour remaining in the tumour bed). [1] Bex A et al. Efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx), in 2022 *ASCO Genitourinary Cancers Symposium*. Journal of Clinical Oncology, Volume 40, Number 6_suppl, https://doi.org/10.1200/JCO.2022.40.6_suppl.2. Clinical trial information: NCT03341845. Research Sponsor: Pfizer, CellCarta, The Netherlands Cancer Institute and Queen Mary University London.

Genomic characterization of baseline and post-progression tumors in IMmotion010, a randomized, phase 3 study of adjuvant (adj) atezolizumab (atezo) vs placebo (pbo) in patients (pts) with high-risk localized renal cell carcinoma (RCC).

Sumanta Kumar Pal, Laurence Albiges, Axel Bex, Cristina Suárez, Robert Uzzo, Xiaobin Tang, Sarita Dubey, Erik T. Goluboff, Corey Allan Carter, Wenxin Xu, Romain Banchereau, Mahrukh A. Huseni, Brian I. Rini; Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA; Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris Saclay University, Villejuif, 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 (VHIO), Hospital Universitari Vall d´Hebron, Vall d´Hebron Barcelona Hospital Campus, Barcelona, Spain; Fox Chase Cancer Center, Philadelphia, PA; Genentech, South San Francisco, CA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Division of Hematology Oncology, Vanderbilt University Medical Center, Nashville, TN

Background: Although adj atezo did not prolong disease-free survival (DFS) in the IMmotion010 trial, accompanying studies identified post-nephrectomy serum KIM-1 levels to be potentially predictive of benefit with atezo. We investigated whether tissue genomics could complement these findings. **Methods:** Tumors were obtained from patients pre-treatment and (if additional consent obtained) at disease recurrence. Whole transcriptome profiles were generated using TruSeq RNA Access Technology (Illumina). Previously, non-negative matrix factorization (NMF) was performed in a separate phase 3 study in advanced RCC (IMmotion151), establishing 7 molecular subgroups (NMF 1-7) (Motzer *et al* Cancer Cell 2020). For each IMmotion010 tumor, we derived signature scores dichotomized at the median as well as NMF1-7 subtype using random forest. Clinical outcome was assessed within these groups alone and with the addition of baseline serum KIM-1 levels, dichotomized into KIM-1 high ($KIM\text{-}1^{H}$) and KIM-1 low ($KIM\text{-}1^{L}$) using the previously established cutoff of 86 pg/mL. Where possible, we sought to characterize the evolution of molecular profiles at disease recurrence. **Results:** Baseline tissue was obtained from 754 pts, reflecting 97% of the intention-to-treat population. Tumors from $KIM\text{-}1^{H}$ patients were enriched in myeloid, granulocyte and proliferation gene signatures at baseline. Among 722 pts for whom both serum KIM-1 and NMF subtype could be characterized, pts in cluster 6 (stromal/proliferative) appeared to derive benefit from atezo (n=50) (Table). Across all patients, no difference in outcome was observed among baseline $Teff^{H}$ and $Teff^{L}$ subsets. Within the $KIM\text{-}1^{H}$ population, $Teff^{H}$ tumors were associated with longer DFS with atezo vs pbo. Paired baseline/recurrence tissue was obtained from 80 pts (atezo: 49; pbo: 31). At recurrence, tumors exhibited increased stromal and proliferation gene signatures, regardless of treatment, reflected in an increased proportion in NMF6 (baseline: 6%; progression: 22%). Exploratory analyses also revealed a decreased MHC-I signature after treatment with atezo. **Conclusions:** This is the first report of tissue genomic profiling in a phase 3 adjuvant immune checkpoint inhibitor study in RCC. While certain molecularly defined subsets may carry predictive value, serum KIM-1 remains the most robust predictor of outcome with atezo. Analyses of progression biopsies highlight an evolution in genomic profile and offer insights into mechanisms of relapse. Clinical trial information: NCT03024996. Research Sponsor: F. Hoffmann-La Roche Ltd.

Subgroup	n	DFS HR
Serum KIM-1		
$KIM\text{-}1^{H}$	290	0.7*
$KIM\text{-}1^{L}$	443	1.13
T-effector signature		
$Teff^{H}$	367	0.87
$Teff^{L}$	366	0.97
NMF subtype		
NMF1	82	1.14
NMF2	271	1.04
NMF3	131	0.96
NMF4	62	0.88
NMF5	60	0.77
NMF6	50	0.25*
NMF7	66	1.62
T-effector signature in $KIM\text{-}1^{H}$ pts		
$KIM\text{-}1^{H}$ $Teff^{H}$	147	0.59*
$KIM\text{-}1^{H}$ $Teff^{L}$	143	0.93

*$P<0.05$.

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An integrative analysis of circulating and tumor microenvironment (TME) determinants of patient response in the Checkmate 9ER (CM 9ER) trial of nivolumab and cabozantinib (NIVO+CABO) in advanced renal cell carcinoma (aRCC).

David A. Braun, Sai Vikram Vemula, Daniel Cook, Aparajita Verma, Patricia E. Carrigan, Kimberly A. Kelly, Toni K. Choueiri, Saurabh Gupta; Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; Bristol Myers Squibb, Princeton, NJ; SimBioSys, Inc., Chicago, IL; 320 N. Sangamon Street 7th floor, Chicago, IL; University of Virginia School of Medicine, Charlottesville, VA; Dana-Farber Cancer Institute, Boston, MA

Background: The CM 9ER trial demonstrated increased objective response rate (ORR), progression-free and overall survival in patients with aRCC treated with NIVO+CABO compared to sunitinib (SUN). For vascular modulating therapies (e.g. CABO and SUN) and immunotherapies (like NIVO), the state of the TME and activity of stromal cells can modulate tumor response to therapy. **Methods:** We investigated how the TME and circulating factors were associated with response to NIVO+CABO using pre-treatment tumor PD-L1 staining, human interpretable features (HIF) derived from H&E tissue sections, circulating immune cell populations quantified by flow cytometry, and circulating extracellular matrix (ECM) markers quantified by competitive ELISAs from 150 patients (23% of ITT) enrolled in CM 9ER. We employed principal component analysis, varimax rotation, and Feature Set Enrichment Analysis (FSEA) to identify a subset of biological measurements capturing 85% of the data variability. We constructed a logistic regression model to associate the most variable features with patient response (ORR per BICR) to NIVO+CABO or SUN therapy. **Results:** An unbiased clustering and feature extraction approach was used to identify measurements contributing to multi-modal variability in the TME across 150 patients (~4000 biological measurements reduced to 16 highly informative measurements): PD-L1 staining, 4 ECM markers, 4 PBMC markers, and 7 H&E HIF features. A final binary logistic regression model was built employing lasso regularization to associate these 16 features to short-term response to NIVO+CABO or SUN while minimizing spurious associations. Based on these regression models, the ECM marker VICM, a citrullinated fragment of vimentin released by matrix metalloproteases, and which measures macrophage activity and immune status, was prognostic across both therapies. Logistic regression models that integrated highly informatic features had AUCs of 0.76 for NIVO+CABO model and 0.72 for the SUN model. Within the NIVO+CABO arm, this integrative model uncovered high VICM (and therefore anti-tumor macrophage polarization), high PD-L1 staining, high plasma cell numbers and high cancer cell numbers at the epithelial stromal interface, low levels of circulating fragment of C-terminal type VIa3 collagen (Pro-C6), and low percentages of circulating regulatory (Foxp3+ CD4+) T cells as determinants of therapeutic response. **Conclusions:** Taken together, these findings indicate that the state of the tumor microenvironment and circulating factors together have an effect on patient responsiveness to NIVO+CABO in aRCC and provides a framework for integrative analysis for biomarker discovery.
Research Sponsor: None.

Gut-associated checkpoint as a prognostic biomarker in metastatic renal cell carcinoma (mRCC): Results from a randomized first-line clinical trial.

Renee Maria Saliby, Marc Machaalani, Caiwei Zhong, Carolina Alves Costa Silva, Chris Labaki, Eddy Saad, Clara Steiner, Emre Yekeduz, Marc Eid, Wassim Daoud Khatoun, Maxine Sun, Ti Cai, David A. Braun, Wenxin Xu, Lisa Derosa, Gwo-Shu Mary Lee, Wanling Xie, Laurence Albiges, Laurence Zitvogel, Toni K. Choueiri; Yale Cancer Center, New Haven, CT; Dana-Farber Cancer Institute, Boston, MA; Oncoclinicas, Rio De Janeiro, Brazil; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; EMD Serono Research and Development Institute, Billerica, MA; Center of Molecular and Cellular Oncology, Yale University, New Haven, CT; Gustave Roussy Cancer Campus (GRCC), ClinicObiome, Villejuif, France; Gustave Roussy, Paris Saclay University, Paris, France; Institut Gustave Roussy, Villejuif, France; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: The gut microbiota modulates anti-cancer immune response and therefore benefit to immune checkpoint inhibitors (ICIs). Gut dysbiosis impacts the MadCAM-1/$\alpha4\beta7$ axis leading to recirculation of immunosuppressive $\alpha4\beta7$+Tr17 cells into tumors. From mechanistic insight to biomarker development, soluble MAdCMA-1 (sMAdCAM-1) is a circulating surrogate marker of gut dysbiosis. We aim to develop sMAdCAM-1 as a prognostic biomarker to ICI-based therapy in patients (pts) with mRCC. **Methods:** Using a Luminex assay, sMAdCAM-1 levels were measured in available plasma samples at baseline from 612 pts (69% of the intent-to-treat population) from the phase III JAVELIN Renal 101 trial (NCT02684006), which compared avelumab + axitinib with sunitinib in previously untreated mRCC pts. sMAdCAM-1 was examined on the original, per 10^4-scaled, and log-transformed scales. Linear assumption was visually checked by deviance residual and restricted cubic splines (RCS) plots. Optimal cut-off value was established based on the maximum log-rank statistic. Cox regression models were used to assess associations with progression-free survival (PFS) and overall survival (OS). The discrimination of the fitted model was assessed by time-dependent AUC index. **Results:** Higher sMAdCAM-1 levels were associated with improved PFS (median: 13.9 [11.3 - 6.6] vs 8.4 [6.0 - 9.9] months) and OS rate (at 18 months: 84.2% [80.2 - 87.4] vs 68.1% [59.2 - 75.5]). These associations remained after adjusting for IMDC risk groups (Table 1). The optimal cutoff was 180 ng/ml (25% percentile) based on the OS outcome in the whole population. Residual and RCS plots further confirmed a non-linear relationship of sMAdCAM-1 levels with OS and PFS. Median follow up was 18.9 months. The prognostic model incorporating IMDC + sMAdCAM-1 demonstrated a significant improvement in the AUC at 18 months compared to IMDC alone (0.72 vs 0.68; p=0.01). These associations were independent of study arm. **Conclusions:** Higher sMAdCAM-1 is associated with improved outcomes to 1st line regimens in mRCC. sMAdCAM-1 may have an added prognostic value to IMDC. As a diagnostic test of gut dysbiosis, it might guide the selection of pts eligible to microbiota-modulating strategies. The validation in two independent datasets and multi-omics correlation (i.e. fecal metagenomics) are ongoing under an international collaboration network. Research Sponsor: None.

Association of MAdCam-1 with clinical outcomes using Cox regression model.

Parameters	PFS HR (95% CI)		OS HR (95% CI)	
Favorable	Ref		Ref	
Intermediate	1.77 (1.31- 2.39)	<0.001	3.01 (1.60 - 5.66)	<0.001
Poor	2.88 (1.99 - 4.17)	<0.001	7.91 (4.02 - 15.56)	<0.001
sMAdCAM-1(high vs low)	0.75 (0.59 - 0.96)	0.021	0.59 (0.41 - 0.85)	0.004

LBA4513 **Rapid Oral Abstract Session**

ENLIGHTED phase 3 study: Interim results of efficacy and safety of padeliporfin vascular targeted photodynamic therapy (VTP) in the treatment of low-grade upper tract urothelial cancer (LG UTUC).

Vitaly Margulis, Ronald P. Kaufman Jr., Gautier Marcq, Asaf Shvero, Neal D. Shore, Sarah P. Psutka, Edward M. Uchio, Hooman Djaladat, Jay D. Raman, Ahmad Shabsigh, Marc Colombel, Marcos Aller, Steffen Rausch, Robert Grubb, Axelle Mroz, Natalia Kudinova, Yaniv Cohen, Genia Alpert, Avigdor Joshua Scherz, Jonathan Coleman; UT Southwestern Medical Center, Dallas, TX; Albany Medical College, Albany, NY; Lille University Hospital, Lille, France; "Chaim Sheba" Medical Center, Ramat Gan, Israel; Carolina Urologic Research Center, Myrtle Beach, SC; Department of Urology, University of Washington, Seattle, WA; Department of Urology, University of California, Irvine Medical Center, Orange, CA; Institute of Urology, USC Norris Cancer Center, Laton, CA; Pennsylvania State University Hershey College of Medicine, Hershey, PA; Ohio State University Comprehensive Cancer Center, Columbus, OH; Hopital Edouard Herriot, Lyon, France; Hospital Universitario de A Coruna, Coruna, Spain; Department of Urology, Eberhard Karls University, Tübingen, Germany; Medical University of South Carolina, Charleston, SC; Steba France SAS, 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

Five-year follow-up results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab (pembro) for the treatment of clear cell renal cell carcinoma (ccRCC).

Naomi Balzer Haas, Thomas Powles, Piotr Tomczak, Se Hoon Park, Balaji Venugopal, Stefan N. Symeonides, Tom Ferguson, Wayne Yen Hwa Chang, Jae Lyun Lee, Piotr Sawrycki, Naveed Sarwar, Howard Gurney, Marine Gross-Goupil, John M. Burke, Gury K. Doshi, Jerry Cornell, Joseph E. Burgents, Rodolfo F. Perini, Toni K. Choueiri; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute and Queen Mary University of London, London, United Kingdom; Poznan University of Medical Sciences, Poznan, Poland; Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; Beatson West of Scotland Cancer Centre and University of Glasgow, Glasgow, United Kingdom; Edinburgh ECMC, Edinburgh Cancer Centre and University of Edinburgh, Edinburgh, United Kingdom; Department of Medical Oncology, Fiona Stanley Hospital, Perth, Western Australia, Australia; Taipei Veterans General Hospital, Taipei, Taiwan; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Provincial Hospital in Torun, Torun, Poland; Imperial College Healthcare NHS Trust, London, United Kingdom; Macquarie University, Sydney, NSW, Australia; Centre Hospitalier Universitaire de Bordeaux - Hôpital Saint-André, Bordeaux, France; Rocky Mountain Cancer Centers, Aurora, CO; Texas Oncology, US Oncology Research, Woodlands, TX; Merck & Co., Inc., Rahway, NJ; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: KEYNOTE-564 (NCT03142334) established pembro monotherapy as the first adjuvant regimen to significantly improve both disease-free survival (DFS) and overall survival (OS) vs placebo (pbo) after surgery for participants (pts) with ccRCC at increased risk of recurrence. We present results from the fourth prespecified interim analysis with a minimum follow-up of 5 yrs. **Methods:** KEYNOTE-564 is a randomized, double-blind, pbo-controlled, phase 3 study, which enrolled adults with ccRCC with intermediate-high (pT2 Gr 4 or sarcomatoid, or pT3 any Gr, N0 M0) or high (pT4 any Gr, N0 M0, or any pT and Gr, N+ M0) risk of recurrence or M1 with no evidence of disease (NED) who had nephrectomy and/or metastasectomy ≤12 wks prior to 1:1 randomization to pembro 200 mg or pbo IV Q3W. Treatment continued for ~1 yr (17 cycles) or until recurrence, intolerable AEs, or physician decision to discontinue treatment. The primary endpoint was DFS by investigator; the key secondary endpoint was OS. The study met its DFS and OS objectives at earlier analyses; thus, no subsequent formal statistical testing occurred. AEs were collected for 30-90 days after treatment cessation depending on severity, with serious treatment-related AEs collected regardless of timing. **Results:** A total of 994 pts were randomized to pembro (n = 496) or pbo (n = 498). The median follow-up time to data cutoff date of 25 Sept 2024 was 69.5 mo (range, 60.2–86.9). All pts completed or discontinued study treatment ≥3 years earlier. 188 DFS events in the pembro group and 241 in the pbo group had occurred. Median DFS was not reached (NR) vs 68.3 mo, respectively (HR 0.71, 95% CI 0.59–0.86); estimated DFS rate at 5 yrs was 60.9% vs 52.2%. 68 OS events in the pembro group and 99 in the pbo group had occurred. Median OS was NR in both arms (HR 0.66, 95% CI 0.48–0.90); estimated OS rate at 5 yrs was 87.7% vs 82.3%, respectively. DFS and OS outcomes were consistent across key subgroups, including by prespecified risk and sarcomatoid features (Table). No new serious treatment-related AEs have been reported for ≥3 years. **Conclusions:** With ≥5 yrs of follow-up, the benefits observed with adjuvant pembro vs pbo are consistent with prior analyses, including in all subgroups. No new serious treatment-related safety signals occurred. Adjuvant pembro remains a standard-of-care option for patients with ccRCC at increased risk of recurrence. Clinical trial information: NCT03142334. Research Sponsor: This study was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

		Prespecified risk subgroups			Sarcomatoid features	
	All pts	Intermediate-high	High	M1 NED	Present	Absent
N	994	855	77	57	111	829
DFS events	429	342	49	37	59	339
DFS HR	0.71	0.75	0.61	0.48	0.56	0.75
(95% CI)	(0.59–0.86)	(0.61–0.93)	(0.35–1.08)	(0.25–0.92)	(0.33–0.96)	(0.60–0.92)
OS events	167	131	22	13	23	130
OS HR	0.66	0.65	0.86	0.36	0.67	0.64
(95% CI)	(0.48–0.90)	(0.46–0.92)	(0.37–1.98)	(0.11–1.18)	(0.29–1.56)	(0.45–0.91)

4515 Rapid Oral Abstract Session

Zanzalintinib (zanza) + nivolumab (nivo) ± relatlimab (rela) in patients (pts) with previously untreated clear cell renal cell carcinoma (ccRCC): Results from an expansion cohort of the phase 1b STELLAR-002 study.

Jad Chahoud, Bradley Alexander McGregor, Oscar Reig Torras, Pedro C. Barata, Jonathan Alexander Chatzkel, Simon Yuen Fai Fu, Daniel Castellano, Pablo Maroto-Rey, Julia Martinez Perez, Philippe Barthelemy, Joanna Wojcik-Tomaszewska, Benjamin Garmezy, Marta González Cordero, Mohan Liu, Xinyu Wang, John Russell, Lana Andrianova, Neil J. Shah; Moffitt Cancer Center, Tampa Bay, FL; Dana-Farber Cancer Institute, Boston, MA; Hospital Clínic of Barcelona, and Translational Genomics and Targeted Therapies in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; University Hospitals Seidman Cancer Center, Cleveland, OH; University of Florida/UF Health Cancer Center, Gainesville, FL; University of Auckland, Auckland, New Zealand; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Hospital Universitario Virgen del Rocío, Seville, Spain; Strasbourg University, Institut de Cancérologie de Strasbourg Europe, Strasbourg, France; Provincial Center of Oncology in Gdańsk, Gdańsk, Poland; Sarah Cannon Research Institute, Nashville, TN; Hospital Universitario de Badajoz, Badajoz, Spain; Bristol Myers Squibb, Lawrence, NJ; Exelixis, Inc., Alameda, CA; Memorial Sloan Kettering Cancer Center, New York, NY

Background: VEGFR-targeted tyrosine kinase inhibitors (TKIs) in combination with immune checkpoint inhibitors (ICIs) are standard of care for previously untreated metastatic ccRCC. Zanza (XL092) is a novel, oral, multi-targeted TKI of VEGFR, MET, and TAM kinases (TYRO3, AXL, MER), with a short half-life that may have an improved therapeutic index. In the phase 1 STELLAR-001 study, the tolerability profile of single-agent zanza was manageable and anti-tumor activity was observed in patients with previously treated advanced ccRCC (Pal et al, IKCS NA 2023). STELLAR-002 (NCT05176483) is a phase 1b, open-label study evaluating the tolerability and activity of zanza alone and in combination with ICIs in pts with advanced solid tumors. Here, data from the expansion cohort of pts with previously untreated ccRCC receiving zanza + nivo ± rela are presented. **Methods:** Adult patients with unresectable advanced or metastatic (adv/met) ccRCC of any IMDC risk, and no prior systemic anticancer therapy for adv/met ccRCC were enrolled into one of two non-randomized arms. Patients received zanza 100 mg orally with either nivo 480 mg IV every 4 weeks (q4w) or nivo/rela 480/480 mg IV q4w (fixed-dose combination). Primary endpoints were investigator-assessed ORR per RECIST 1.1 and safety. **Results:** In the zanza + nivo arm (n = 40), 75% had intermediate or poor IMDC risk disease. After median follow-up of 16.1 months, the ORR was 63% (4 complete responses [CRs], 21 partial responses [PRs]), and disease control rate (DCR: CR+PR+SD) was 90%. The 6- and 12-month PFS rates were 83.2% and 64.2%, respectively. The most common any grade (G) treatment-emergent adverse events (TEAEs) were diarrhea (78%), hypertension (58%), and nausea (58%). The most common G3/4 AEs related to zanza were hypertension (30%) and diarrhea (15%). Treatment-related palmar-plantar erythrodysesthesia (PPE) was reported in 28% (8% G3, 0% G4). Two (5%) pts discontinued both study treatments due to treatment-related AEs (TRAEs). Median average daily zanza dose was 49.5 mg (range: 26-100). In the zanza + nivo/rela arm (n = 40), 70% had intermediate or poor IMDC risk disease. After a median follow-up of 11.9 months, the ORR was 33% (1 CR, 12 PRs) and DCR was 90%. The 6- and 12-month PFS rates were 80.2% and 58.8%, respectively. The most common any G TEAEs were diarrhea (60%) and nausea (50%). The most common G3/4 AE related to zanza was hypertension (13%). Treatment-related PPE occurred in 5% (0% G3/4). Seven (18%) pts discontinued all study treatment due to TRAEs. Median average daily zanza dose was 54.9 mg (range: 31-100). No G5 TRAEs occurred in either arm. **Conclusions:** First-line zanza had acceptable tolerability in combination with nivo or nivo/rela with a low rate of PPE; zanza+nivo showed promising preliminary activity in pts with adv/met ccRCC. Clinical trial information: NCT05176483. Research Sponsor: Exelixis, Inc.

Ipilimumab and nivolumab in patients with metastatic clear cell renal cell carcinoma (mccRCC) treated on the phase 3 PDIGREE (Alliance A031704) trial: Results from Step 1 analysis.

Tian Zhang, Karla V. Ballman, Bradley Alexander McGregor, Helen Moon, Marc Ryan Matrana, Robert S. Alter, Abhishek Tripathi, Yuanquan Yang, Rana R. McKay, Deepak Kilari, Ulka N. Vaishampayan, Hamid Emamekhoo, Elaine T. Lam, Suzanne Cole, Tracy L. Rose, Stephanie A. Berg, Alan Tan, Michael J. Morris, Daniel J. George, Toni K. Choueiri; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Mayo Clinic, Rochester, MN; Dana-Farber Cancer Institute, Boston, MA; SCPMG, Kaiser Permanente, Riverside, CA; Ochsner Health, New Orleans, LA; Hackensack University Medical Center, Hackensack, NJ; University of Okahoma Health Sciences Center, Oklahoma City, OK; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Moores Cancer Center, University of California San Diego, La Jolla, CA; Department of Medicine, Division of Hematology and Oncology, The Medical College of Wisconsin, Milwaukee, WI; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; University of Wisconsin-Madison, Madison, WI; University of Colorado Cancer Center, Aurora, CO; Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Vanderbilt-Ingram Cancer Center, Nashville, TN; Memorial Sloan Kettering Cancer Center, New York, NY; Duke Cancer Institute, Duke University School of Medicine, Durham, NC; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Ipilimumab/nivolumab (ipi/nivo) is a standard of care first-line treatment (tx) for patients (pts) with mccRCC; however, ideal timing of subsequent immunotherapy txs are not well defined. We performed an analysis of patients initially treated with ipi/nivo and subsequent cohort assignments on PDIGREE (A031704). **Methods:** The PDIGREE trial treated pts with IMDC intermediate/poor risk mccRCC with first-line ipi/nivo (Step 1) at NCTN sites (categorized as academic (A), academic regional (R), and community (C)). Subsequent management was based on iRECIST responses at 12 weeks: pts with complete response (CR) received 1-year nivo maintenance; pts with progressive disease (PD) received cabozantinib (cabo) monotherapy, pts with non-CR/non-PD were randomized to nivo with or without cabo (for primary endpoint of overall survival [OS], target sample size was 1175). Enrollment was held when the randomized sample target was reached. Pts with unresolved toxicity at week 22 were managed off protocol. Step 1 pt demographics, assignments into Step 2, and adverse event (AE) data are presented. Descriptive statistics were used, and cohorts were compared using a chi-square test. These data were released with DSMB approval and do not inform the primary OS endpoint (1EP). **Results:** From May 2019 to May 2024, 1111 pts were enrolled and treated with ipi/nivo. Pt characteristics included median age 64.0 years (range 29.0-86.0); 819 (73.7%) males; White (85.1%), Hispanic (10.4%), Black (4.2%), and American Indian/Native Hawaiian (1.3%); 849 (76.8%) intermediate risk/257 (23.2%) poor risk; 458 (41.2%) at Academic, 113 (10.2%) at Regional, and 540 (48.6%) at Community centers; and 603 (54.3%) with *de novo* metastases. 364 pts (33%) stopped tx in Step 1: 160 (44%) for AEs, 46 (13%) for PD/clinical PD/suspected PD, 42 (12%) withdrawals, 39 (11%) alternative txs, 37 (10%) deaths on the study, 12 (3%) other complicating disease, 8 (2%) MD decision and 19 (5%) other reasons. Of the 37 deaths, 15 (1.4%) grade 5 SAEs were reported, 6 of which were due to PD. Of 747 (67%) pts registered to Step 2 at 3 months, 9 (1.2%) achieved CR, and 141 (18.9%) pts were assigned to the PD cohort. 597 pts (80%) were randomized for the 1EP, notable with fewer pts with poor risk [(21 vs 27%, p = 0.01] and bone metastases [24.5% vs 34.2%, p = 0.0007] compared to Step 1 pts who discontinued tx. Gr 3/4 tx-related AEs in 314/1093 (29%) evaluable pts included diarrhea/colitis (8%), transaminase elevation (3%), rash (2%), adrenal insufficiency (2%), fatigue (2%), and hypophysitis (1%). **Conclusions:** The PDIGREE trial enrolled a representative US-based population with mccRCC. Step 1 pt characteristics and associated outcomes with induction ipi/nivo reveal new insights into the tolerability and tx response of 1L ipi/nivo. Clinical trial information: NCT03793166. Research Sponsor: Alliance Group: U10CA180821, U10CA180882; SWOG: U10CA180888; https://pubs.alliancefound.org/acknowledgments.

Sasanlimab in combination with bacillus Calmette-Guérin (BCG) in BCG-naive, high-risk non–muscle-invasive bladder cancer (NMIBC): Event-free survival (EFS) subgroup analyses based on disease stage from the CREST study.

Thomas Powles, Neal D. Shore, Jens Bedke, Matthew D. Galsky, Joan Palou, Hailong Hu, Evanguelos Xylinas, Javier Puente, Jason Hafron, Michele Lodde, Alketa Hamzaj, Julia Brinkmann, Anna Maria Calella, Rossano Cesari, Jennifer Vermette, Caimiao Wei, Gary D. Steinberg; Barts Cancer Centre, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, London, United Kingdom; Carolina Urologic Research Center, Myrtle Beach, SC; Department of Urology & Eva Mayr-Stihl Cancer Center, Stuttgart, Germany; The Tisch Cancer Institute, Mount Sinai, New York, NY; Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain; The Second Hospital of Tianjin Medical University, Tianjin, Tianjin, China; Bichat-Claude Bernard Hospital, Assistance Publique–Hôpitaux de Paris, Université Paris Cité, Paris, France; Hospital Universitario Clínico San Carlos, Madrid, Spain; Michigan Institute of Urology, Troy, MI; Laval University, Quebec City, QC, Canada; UOC Oncologia Arezzo, Ospedale San Donato, Arezzo, Italy; Pfizer Pharma GmbH, Berlin, Germany; Pfizer SRL, Rome, Italy; Pfizer SRL, Milano, Italy; Pfizer, Inc., Cambridge, MA; Pfizer Inc, Groton, CT; Department of Urology, Rush University, Chicago, IL

Background: Sasanlimab in combination with BCG (induction [IND] and maintenance [MNT]) significantly improved investigator (INV)-assessed EFS vs BCG (IND and MNT) and had a manageable safety profile in patients (pts) with BCG-naive, high-risk NMIBC, according to the primary analysis results from the phase 3 CREST study. Here, we report exploratory EFS subgroup analyses not previously presented based on disease stage at randomization from Arms A and C. **Methods:** Eligible pts were randomized 1:1:1 to receive sasanlimab in combination with BCG (IND and MNT; Arm A), sasanlimab in combination with BCG (IND; Arm B), or BCG (IND and MNT; Arm C). To assess the impact on efficacy of carcinoma in situ (CIS) and T1 tumors at baseline, post hoc INV-assessed EFS analyses were conducted for the comparison of Arm A vs Arm C. EFS was defined as time from randomization to recurrence of high-grade disease, progression of disease, persistence of CIS (for patients with CIS at randomization), or death due to any cause, whichever occurred first. **Results:** At the data cutoff date (Dec 02, 2024), the median duration of follow-up for EFS was 36.4 and 36.7 months for Arm A and Arm C, respectively. A total of 176 pts with CIS (with or without papillary tumors) were in Arms A and C, 102 of whom had CIS without papillary tumors. A total of 398 pts with T1 tumor were in Arms A and C, 342 of whom had T1 tumor without CIS (Table). Three-year landmark EFS subgroup analyses not previously presented are reported in the table. For patients with CIS, with or without concomitant papillary tumors, the 3-year EFS rate was 83.0% in Arm A and 71.8% in Arm C. For patients with T1 tumors, with or without CIS, the 3-year EFS rate was 81.3% in Arm A and 72.2% in Arm C. **Conclusions:** Sasanlimab in combination with BCG (IND and MNT) improved EFS outcomes in the overall population and in the subgroups of pts with BCG-naive, high-risk NMIBC who had CIS or T1 tumors at randomization. This post hoc analysis further supports the potential of sasanlimab in combination with BCG as a practice-changing treatment in pts with aggressive disease. Clinical trial information: NCT04165317. Research Sponsor: Pfizer Inc.

	Arm A(N=352)		Arm C(N=351)		HR (95% CI) Arm A vs Arm C
	n (%)	36-mo EFS rate, % (95% CI)	n (%)	36-mo EFS rate, % (95% CI)	
All pts		82.1 (77.4-85.9)		74.8 (69.7, 79.2)	0.68 (0.489-0.941)[a]
Tumor type at randomization					
CIS with and without papillary tumors	88(25.0)	83.0 (72.9-89.6)	88(25.1)	71.8 (60.4-80.5)	0.53(0.285-0.982)
CIS without papillary tumors	52(14.8)	81.0 (66.6-89.7)	50(14.2)	75.4 (59.9-85.6)	0.52 (0.233-1.165)
T1 with and without CIS	204(58.0)	81.3 (74.7-86.4)	194(55.3)	72.2 (65.0-78.2)	0.63 (0.406-0.963)
T1 without CIS	178 (50.6)	79.6 (72.1-85.2)	164(46.7)	72.5 (64.6-78.9)	0.70 (0.446-1.109)

[a]Stratified HR; all other HR unstratified.

First results of SURE-02: A phase 2 study of neoadjuvant sacituzumab govitecan (SG) plus pembrolizumab (Pembro), followed by response-adapted bladder sparing and adjuvant pembro, in patients with muscle-invasive bladder cancer (MIBC).

Andrea Necchi, Joep de Jong, James A. Proudfoot, Brigida Anna Maiorano, Antonio Cigliola, Valentina Tateo, Chiara Mercinelli, Michela Ravasi, Elai Davicioni, Marco Moschini, Giorgio Brembilla, Maurizio Colecchia, Francesco De Cobelli, Alberto Briganti, Francesco Montorsi; IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; Erasmus University Medical Center, Rotterdam, Netherlands; Veracyte, Inc., South San Francisco, CA; IRCCS San Raffaele Hospital, Milan, Italy; Oncology Department, IRCCS San Raffaele Hospital, Milan, Italy; Veracyte, Inc., San Diego, CA; Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy; Department of Radiology, IRCCS San Raffaele Hospital, Milan, Italy; Department of Pathology and Laboratory Medicine, IRCCS San Raffaele Hospital, Milan, Italy; Unit of Urology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; IRCCS San Raffaele Scientific Institute, Urological Research Institute (URI), Milan, Italy

Background: Standard of care for MIBC is radical cystectomy (RC) with neoadjuvant chemotherapy (CT), but ~50% of patients (pts) are ineligible for/refuse CT and survival for RC alone is dismal. Neoadjuvant Pembro and SG monotherapies showed activity in MIBC within PURE-01 and SURE-01 studies. SURE-02 (NCT05535218) is a phase 2 study of neoadjuvant SG+Pembro and adjuvant Pembro, including a bladder-sparing approach depending on clinical response. We report results of a prespecified interim analysis. **Methods:** Pts age ≥18 y, ECOG PS 0-1, with histologically confirmed cT2-T4N0M0 MIBC, ineligible/refusing CT, and scheduled for RC received 4 cycles of Pembro 200 mg on D1 and SG 7.5 mg/Kg on D1 and D8, Q3W, followed by postsurgical Pembro x 13 cycles, Q3W. A reTURBT is allowed instead of RC, followed by Pembro x 13 cycles, for pts achieving a clinical complete response (cCR), stringently defined as a negative magnetic resonance imaging (MRI) and no residual viable tumor at reTURBT (ypT0). Primary outcome measure is cCR rate: H0≤30%, H1≥45%. Other outcomes: ypT≤1N0-x rate including pts undergoing RC, safety (CTCAE v.5.0), survival. The total sample size is 48 pts in a 2-stage design, with 23 pts enrolled at first stage (≥7 cCR needed). Decipher Bladder (Veracyte, San Diego, CA) was used for transcriptome-wide analyses of primary TURBT tissue. **Results:** From 10/23 to 01/25, 40 pts were treated and 31 were efficacy evaluable. 20 (64.5%) had a cT2 stage, 12 (38.7%) had a centrally confirmed variant histology. The cCR-rate was 38.7% (N = 12; 95%CI: 21.8-57.8); all these pts underwent a reTURBT; ypT≤1N0-x rate was 51.6% (N = 16). Grade ≥3 treatment-related adverse-events occurred in 4 pts (12.9%), 2 dose omissions of SG and one dose delay (1W) were recorded. No SG dose-reduction was needed. cCR varied by molecular subtype. Transcriptome results were available for 23 pts: complete pathologic (ypT0) responses varied by Genomic Subtyping Classifier (GSC) groups with luminal tumors showing higher ypT0 rates vs non-luminal (73 vs 25%, p = 0.04). Similarly, based on Lund subtypes, genomically unstable (GU) tumors had ypT0 response in 67%, vs 57% for urothelial-like, 20% for basal/squamous and 0% for neuroendocrine-like. Higher stromal signature (> median) was associated with non-ypT0 response (p = 0.004), while neither Trop2 (p = 0.15) nor *TOP1* (p = 0.79) gene expression were associated with ypT0 response. **Conclusions:** Perioperative SG+Pembro revealed a compelling cCR rate, with a manageable safety profile, allowing a bladder preservation in ~40% of pts. Pre-treatment molecular biomarker analyses suggest a unique tumor profile associated with cCR. Overall, SURE-02 interim results support the completion of study accrual and further investigation of SG+Pembro in pts with MIBC. Clinical trial information: NCT05535218. Research Sponsor: Gilead; Merck; Associazione Italiana per la Ricerca sul Cancro (AIRC); IG 27746.

4519 Rapid Oral Abstract Session

9MW2821, a novel Nectin-4 antibody-drug conjugate (ADC), combined with toripalimab in treatment-naïve patients with locally advanced or metastatic urothelial carcinoma (la/mUC): Results from a phase 1b/2 study.

Shusuan Jiang, Hongqian Guo, Hongchen Qu, Yuchen Bai, Benkang Shi, Peng Zhang, Xin Yao, Tie Jun Yang, Hang Huang, Manming Cao, Jun Guo, Xinan Sheng, Jingming Dong, Peipei Wang, Shuhai Wang; Hunan Cancer Hospital, Changsha, China; Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China; Liaoning Cancer Hospital, Shenyang, China; Zhejiang Provincial People's Hospital, Hangzhou, China; Qilu Hospital of Shandong University, Jinan, China; Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Henan Cancer Hospital, Zhengzhou, China; The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; Department of Oncology, Zhujiang Hospital, Southern Medical University, Guangzhou, China; Beijing Cancer Center, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Mabwell (Shanghai) Bioscience Co., Ltd., Shanghai, China

Background: Nectin-4 is an adhesion molecule that is highly expressed in variety of solid tumors. Previous study of 9MW2821 has shown promising efficacy and tolerable toxicity in different advanced cancers, especially in urothelial cancer, cervical cancer, esophageal cancer and breast cancer. Here we report preliminary results of 9MW2821 combined with Toripalimab in treatment-naïve patients with la/mUC. **Methods:** This is an open-label, multicenter, phase 1b/2 study to evaluate the safety and efficacy of 9MW2821 combined with Toripalimab in la/mUC. Patients received 9MW2821 on D1/D8 and Toripalimab on D1, 21 days per cycle. Primary objective was safety, and secondary objectives were efficacy, pharmacokinetics and immunogenicity. **Results:** 40 treatment-naïve patients with la/mUC were enrolled and received the combination therapy of 9MW2821(1.25mg/kg) and Toripalimab(240mg). Median age was 66.5 years [36-78], and 73% patients were ECOG 1. 55% primary tumor sites were upper tract urothelial carcinoma. As of Dec 19, 2024, ORR was 87.5% [35/40, 95%CI 73.2-95.8], including 7.5% CR rate (comfirmed ORR was 80%). DCR was 92.5% [37/40, 95%CI 79.6-98.4]. Median PFS and DoR were not reached, 6-month PFS rate and 3-month DoR rate were 79.1% and 100%. Furthermore, ORR of subgroups in liver metastasis, bladder cancer and tumor with negative expression of Nectin-4 were 88.2%, 94.4%, 100%, respectively. These showed that different subgroups of treatment-naïve patients could benefit from the combination therapy of 9MW2821 and Toripalimab. The most common treatment-related AEs(TRAEs) were grade 1 or 2, 23.8% patients experienced TRAEs of grade 3 or above, including neutrophil count decreased (7.1%), rash (4.8%), ALT increased (4.8%), etc. No TRAEs led to death occurred. No new safety signals of 9MW2821 or Toripalimab were observed in this study. **Conclusions:** 9MW2821 combined with Toripalimab in treatment-naïve patients with la/mUC demonstrated remarkable efficacy and well-tolerated safety profile. A pivotal phase 3 study is ongoing currently. Clinical trial information: NCT06079112. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

CLONEVO: Preoperative abemaciclib for cisplatin-ineligible muscle-invasive bladder cancer (MIBC) with molecular response assessment.

Bishoy Morris Faltas, Mohamed Osman, Mark Gordon Evans, Daniel Margolis, Cora N. Sternberg, Jones T. Nauseef, Ana M. Molina, David M. Nanus, Neal A. Patel, Rohit K. Jain, Juan Miguel Mosquera, Philip Abbosh, Manuel Hidalgo, Nicolas Robine, William F Hooper, Olivier Elemento, Namrata Peswani, Suzanne Cole, Douglas Scherr, Scott T. Tagawa, Weill Cornell EIPM; Weill Cornell Medicine, New York, NY; Caris Life Sciences, Irving, TX; Weill Cornell Imaging at NewYork-Presbyterian, New York, NY; Weill Cornell Medicine, NewYork-Presbyterian Hospital, New York, NY; Convergent Therapeutics, Cambridge, MA; Weill Medical College of Cornell University/NewYork-Presbyterian, New York, NY; Fox Chase Cancer Center, Philadelphia, PA; NewYork-Presbyterian, Weill Cornell Medicine, New York, NY; New York Genome Center, New York, NY; UT Southwestern Medical Center, Dallas, TX; Department of Urology, Weill Cornell Medical College & New York-Presbyterian Hospital, New York, NY

Background: Up to 40% of MIBC patients are ineligible to receive standard neoadjuvant cisplatin-based chemotherapy creating a significant unmet need. Based on our prior findings of frequent cell cycle alterations, we conducted the first window-of-opportunity, investigator-initiated trial of the CDK4/6 inhibitor abemaciclib (abema) followed by radical cystectomy (RC) in MIBC (NCT03837821). **Methods:** Eligibility was MIBC appropriate for RC and cisplatin-ineligibility or refusal. Planned treatment was abema (200mg BID PO) for 4-8 weeks prior to RC. We planned to enroll 20 patients (accounting for 20% attrition). 16 evaluable patients provided 80% power to detect 0.75 effect size (α = 0.05, r = 0.5 between pairs). Whole-exome (WES) and RNA sequencing of pre- and post-abema tissues and serial evaluation of ctDNA WES were performed on Caris Life Sciences' platform. **Results:** 20 patients received abema for a median of 36 days. Median age was 73, 16/20 were males, and 5/20 had cT4. 3 didn't undergo RC, and 1 withdrew consent. Abema resulted in pathologic complete response in 18.8% (3/16) and downstaging in 31.3% (5/16). No unexpected safety signals were detected. Grade 3 abema-related adverse events included anemia (4/20), abdominal pain (1/20) and diarrhea (1/20). Imaging Mass Cytometry of pre- and post-abema tissues showed a significant reduction in RB1 phosphorylation after abema confirming on-target activity. Variant allele frequency of somatic mutations significantly decreased after abema by 20.5% (p = 0.04), confirming its role in decreasing tumor burden. Serial ctDNA showed a significant reduction in tumor fraction (TF) following abema by 28.6%. Post-TURBT pre-abema TF increased but rapidly decreased within 2 weeks of abema (19.36%), confirming TF reduction was driven by abema not TURBT. Patients with CCND1 amplification had the most significant decrease in TF (63.8%) highlighting CCND1 as a potential response biomarker. Abema significantly downregulated MKI67, CCNA2, and PCNA proliferation markers with log-fold changes of -1.2, -0.7, and -0.6. Gene set enrichment analysis showed significant downregulation of E2F targets and G1/S transition pathways. Patients who achieved pathologic downstaging had significant decrease in E2F pathway activity (-1.6 vs. -0.4, p = 0.01) confirming that abema suppressed E2F-dependent cell proliferation. Interestingly, abema significantly inhibited homologous recombination repair of double-strand DNA break (DSBs) (FDR = 0.001), particularly TOPBP1 and RAD51. **Conclusions:** This first trial of short-term preoperative abema in MIBC demonstrated promising efficacy and tolerability while modulating cell cycle-dependent pathways. Our findings support future trials investigating sequential abema with antibody-drug conjugates such as enfortumab vedotin, where abema's effects on DSBs repair augment treatment response. Clinical trial information: NCT03837821. Research Sponsor: Eli Lilly.

AREN1721, a randomized phase 2 trial of axitinib+nivolumab combination therapy vs. single agent nivolumab for the treatment of TFE/translocation renal cell carcinoma (tRCC) across all age groups, an NCI National Clinical Trials Network (NCTN) phase 2 study.

Nicholas Cost, Lindsay A. Renfro, Matthew R. Zibelman, Ana M. Molina, Mamta Parikh, Luke E. Pater, Ian Tfirn, Elizabeth A. Mullen, Peter F. Ehrlich, Elisabeth T. Tracy, John A. Kalapurakal, Jeffrey Dome, James I. Geller; Denver Childrens, Denver, CO; University of Southern California, Los Angeles, CA; Fox Chase Cancer Center, Philadelphia, PA; Weill Cornell Medical College, NewYork-Presbyterian Hospital, New York, NY; University of California, Davis Comprehensive Cancer Center, Sacramento, CA; University of Cincinnati, Cincinnati, OH; University of Florida College of Medicine, Jacksonville Florida, FL; Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA; University of Michigan Hospital, Ann Arbor, MI; Division of Pediatric Surgery, Duke Children's Hospital and Health Center, Durham, NC; Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; Children's National Hospital, Washington, DC; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background: tRCC accounts for approximately 50% of pediatric RCC and 1-5% of RCC cases overall. tRCC, driven by *TFE3* or *TFEb* fusions or amplifications (*TFEb*), are often aggressive with no existing standard for systemic therapy. **Methods:** AREN1721 was a prospective randomized COG-led NCTN phase 2 trial of nivolumab/axitinib combination therapy vs. axitinib alone (closed early for feasibility) vs. nivolumab alone in children and adults with advanced unresectable or metastatic tRCC. Prior exposure to anti-PD1/PDL1 therapies or axitinib was prohibited. The primary endpoint was progression-free survival (PFS), defined as the time from randomization to the earliest of disease progression based on immune-modified RECIST criteria or death. The final protocol version targeted enrollment of 28 eligible patients to detect a hazard ratio (HR) of 0.40 for the comparison of nivolumab/axitinib vs. nivolumab alone using a one-sided log-rank test with alpha = 0.15. **Results:** Despite aggressive approaches for trial recruitment, AREN1721 was closed after enrolling 15 patients (13 eligible) from 2019 to 2023 secondary to poor accrual. Median age 16 years (range 7-42) with 9/13 age $<$ 18 years; 9/13 were male. Six patients were randomized to nivolumab+axitinib, 2 to axitinib alone, and 5 to nivolumab alone. There were no unexpected toxicities. Thirty-three percent of patients randomized to nivolumab+axitinib experienced partial response, compared to 0% in the other arms, and 0% of patients on the combination arm experienced primary disease progression. Addition of axitinib to nivolumab significantly improved PFS (p = 0.0004), extending median PFS from 1.8 to 10.5 months. Overall survival also improved (p = 0.003) with the addition of axitinib. **Conclusions:** Nivolumab+axitinib combination therapy was statistically more active than nivolumab single agent therapy, which itself was inactive. Whether anti-PD1 pathway inhibitors add benefit to anti-VEGF therapy for tRCC remains to be determined. Optimizing trial recruitment is critical for this rare but aggressive cancer. Clinical trial information: NCT03595124. Research Sponsor: U.S. National Institutes of Health; U10CA098543; :U10CA180886; U10CA098413, U10CA180899.

Descriptive statistics by arm.

Characteristic	Arm A: Axitinib/ Nivolumab N = 6	Arm B: Axitinib N = 2	Arm C: Nivolumab N = 5	Overall N = 13	p-value[1]
Age (Years)					0.715
Mean (SD)	18 (9)	19 (6)	18 (14)	18 (10)	
Median (Q1, Q3)	16 (10, 21)	19 (15, 23)	15 (12, 16)	16 (12, 21)	
Min, Max	9, 32	15, 23	7, 42	7, 42	
Age Category					>0.999
Age < 18	4 (67%)	1 (50%)	4 (80%)	9 (69%)	
Age 18+	2 (33%)	1 (50%)	1 (20%)	4 (31%)	
Prior Anti-VEGF therapy	1 (17%)	0 (0%)	1 (20%)		>0.999
No prior systemic therapy	5 (83%)	2 (100%)	4 (80%)	11 (85%)	
Best Overall Response					0.019
Partial Response	2 (33%)	0 (0%)	0 (0%)	2 (15%)	
Stable Disease	4 (67%)	2 (100%)	1 (20%)	7 (54%)	
Progressive Disease	0 (0%)	0 (0%)	4 (80%)	4 (31%)	

[1]Kruskal-Wallis rank sum test; Fisher's exact test.

Ipilimumab/nivolumab versus standard of care in non-clear cell renal cancer: Results of the SUNNIFORECAST trial and potential role of the CPS score and tumor nephrectomy.

Lothar Bergmann, Laurence Albiges, Marit Ahrens, Marine Gross-Goupil, Ekaterini Boleti, Gwenaelle Gravis, Aude Flechon, Marc-Oliver Grimm, Jens Bedke, Philippe Barthelemy, Daniel Castellano, Begoña Mellado, Philipp Ivanyi, Anne Flörcken, Cristina Suárez, Pablo Maroto-Rey, Viktor Grünwald, Iris Burkholder, Arndt Hartmann, John Haanen, Interdisciplinary Working Group Renal Cell Carcinoma (IAGN); University Hospital Frankfurt, Medical Clinic II (Hematology/Oncology), Frankfurt, Germany; Gustave Roussy, Paris Saclay University, Paris, France; University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; Centre Hospitalo-Universitaire, Bordeaux, France; Royal Free London NHS Foundation Trust, London, United Kingdom; Institut Paoli-Calmettes, Aix-Marseille Universite, CRCM, Marseille, France; Centre Léon Bérard, Lyon, France; Friedrich Schiller Universitat, Jena, Germany; University Hospital Tübingen, Tübingen, Germany; Department of Medical Oncology, Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Clínic i Provincial de Barcelona, Barcelona, Spain; Department of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Claudia-von Schilling Comprehensive Cancer Center, Hannover Medical School, Hannover, Germany; Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Department of Hematology, Oncology, and Tumor Immunology, Campus Virchow-Klinikum, Berlin, Germany; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Department of Medical Oncology, Hospital Sant Pau, Barcelona, Spain; Essen University Hospital, Essen, Germany; Department of Nursing and Health, University of Applied Sciences, Saarbruecken, Germany; Institute of Pathology, Universitatsklinikum Erlangen, Friedrich-Alexander-Universitat Erlangen-Nürnberg, Erlangen, Germany; Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Non-clear cell renal cancers (nccRCC) are a rare and heterogeneous group of >20 histological and molecular defined entities. Due to the rarity of these entities, the clinical data are limited and large randomized trials are missing resulting in uncertainties for optimal treatment recommendations. So far, TKI therapy with or without immune checkpoint inhibitors (ICI) are considered standard of care (SOC) options in these diseases. Here we report the results of the academic prospective randomised European trial in therapy-naïve patients with advanced nccRCC entities, which compared ipilimumab/nivolumab (Ipi/Nivo) vs SOC. **Methods:** We randomly assigned patients (pts) with nccRCC in a 1:1 ratio to receive either nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every 3 weeks for 4 doses followed by a flat dose of 240 mg IV every 2 weeks or 480 mg every 4 weeks versus SOC by investigators choice until disease progression or intolerance occurred. Pts were stratified in papillary vs. non-papillary nccRCC and according to IMDC risk score. Central pathology was mandatory to confirm the correct diagnosis of the nccRCC subtype according to the WHO classification 2022.The primary endpoint was the overall survival (OS) rate at 12 months (mos), secondary endpoints were the OS rate at 6 mos and 18 mos, OS, progression-free survival (PFS) and response rate (RR). **Results:** 309 pts (70.9% male, 29.1% female) out of 316 pts were randomized to receive either Ipi/Nivo or SOC. 173 (56.0%) pts were of papillary subtype (pRCC) and 143 (44.0%) pts of non-papillary subtypes, whereas 59 pts had chromophobe (ccRCC), 20 sarcomatoid/rhabdoid, 10 collecting duct, 11 TFE3-rearranged or TFEB-altered RCC and 37 other histological features. According to the IMDC score, 23.9% were of favorable, 51.8% of intermediate and 24.3% of poor risk. The 12 mos OS rate for Ipi/Nivo of 78.3% (95%-CI 70.9%-83.9%) vs 68.3% (95%-CI 60.0%-75.3%) in the SOC arm was statistically significant (p=0.026). Median OS was 33.2 mos for the Ipi/Nivo arm and 25.2 mos for the SOC arm. The ORR of 32.8% vs. 19.4% and the median PFS of 5.4 mos vs 5.7 mos was not statistically significant different between both arms. The explorative endpoint CPS score differed between the various subentities and was associated with an advantage in OS. Pts with a CPS≥1 had an OS-rate at 12 months of 79.3% in the Ipi/Nivo arm vs. 58.3% and a median OS of 38.6 mos vs. 18.8 mos (p=0.007). Furthermore, pts who did not underwent a tumor nephrectomy (possibly due to high risk) had a survival benefit with 26.3 mos in the Ipi/Nivo arm vs 16.5 mos in the SOC arm (p=0.065) in contrast to nephrectomized pts with 38.9 mos vs 34.0 mos. **Conclusions:** The OS-Rate at 12 mos was significantly superior for Ipi/Nivo in comparison to SOC and the primary endpoint was met. Additionally, pts in the Ipi/Nivo arm had a longer median OS, especially those with a CPS≥1. Clinical trial information: NCT03075423. Research Sponsor: None.

Efficacy and safety of second-line cabozantinib ± atezolizumab for patients with advanced renal cell carcinoma after progression on immuno-oncology combinations: Subgroup analysis of CONTACT-03.

Cristina Suárez, Toni K. Choueiri, Laurence Albiges, Martin H. Voss, Bradley Alexander McGregor, Omara Khan, Denise Svendsgaard Williamson, Jose Ricardo Perez-Torrealba, Tasha D. Hall, Sumanta Kumar Pal; Medical Oncology, Vall d´Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d´Hebron, Vall d´Hebron Barcelona Hospital Campus, Barcelona, Spain; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Institut Gustave Roussy, Université Paris Saclay, Villejuif, France; Memorial Sloan Kettering Cancer Center, New York, NY; Roche Product, Welwyn Garden City, United Kingdom; Exelixis, Inc., Alameda, CA; City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Cabozantinib (cabo), a vascular endothelial growth factor receptor-associated tyrosine kinase inhibitor (TKI), is a preferred treatment option for second-line (2L) treatment of advanced renal cell carcinoma (RCC) based on its superior efficacy vs everolimus (Choueiri TK, *N Engl J Med* 2015); however, its activity after contemporary first-line (1L) immuno-oncology (IO) combinations is not well characterized. CONTACT-03 was a large phase 3 study evaluating the efficacy and safety of cabo ± atezolizumab (atezo) after progression on previous IO treatment (Pal SK, *Lancet* 2023). We report the results of a subgroup analysis of the safety and efficacy of 2L cabo ± atezo in patients from CONTACT-03 who received standard of care (SOC) 1L IO-IO or IO-TKI combinations. **Methods:** In CONTACT-03, adults with metastatic RCC whose disease had progressed on IO-based regimens were randomized to cabo (60 mg PO QD) alone or with atezo (1200 mg IV Q3W). This subgroup analysis included patients who had received 1L IO-IO or IO-TKI SOC combinations prior to enrolling in CONTACT-3. Outcomes for 2L treatment included PFS by blinded independent central review (BICR), OS, ORR, duration of response, and safety. **Results:** Of 522 patients, 107 in the cabo arm and 129 in the cabo + atezo arm had received prior treatment with IO-IO (ipilimumab-nivolumab) or IO-TKI (axitinib-avelumab, axitinib-pembrolizumab, or lenvatinib-pembrolizumab). Efficacy outcomes were comparable between treatments (Table). For cabo and cabo + atezo, respectively, median PFS by BICR was 10.3 and 10.2 months, and ORR was 36% and 37%. Grade 3/4 treatment-related adverse events (AEs) were reported in 48% and 58% of patients treated with cabo and cabo + atezo, respectively, treatment-related serious AEs were reported in 13% and 25% of patients, and AEs led to dose modification in 87% and 92% of patients and discontinuation in 5% and 17% of patients, respectively. **Conclusions:** Results from this post-hoc subgroup analysis of CONTACT-03 suggest 2L cabo is effective in patients with advanced RCC previously treated with 1L IO-IO or IO-TKI regimens. Safety was consistent with the overall study. These results can inform clinicians making 2L treatment decisions for patients who have progressed on contemporary 1L IO-containing combinations. Clinical trial information: NCT04338269. Research Sponsor: Exelixis, Inc.

Efficacy outcomes with cabo ± atezo after 1L IO combinations.

	Cabo (n=107)	Cabo + atezo (n=129)
Median PFS by BICR, months (95% CI)	10.3 (7.95, 12.45)	10.2 (8.34, 10.64)
Median OS, months (95% CI)	NE (18.30, NE)	24.2 (20.24, NE)
Best overall response by BICR, %	36	37
Complete response, %	0	0
Partial response, %	36	37
Stable disease, %	50	52
Progressive disease, %	10	5
Not evaluable/missing, %	5	6
Duration of response by BICR, months (95% CI)	15.0 (10.28, NE)	10.5 (7.95, NE)

NE, not estimable.

Comparison of ^{68}Ga-NY104 PET/CT with ^{18}F-FDG PET/CT in patients with metastatic clear cell renal cell carcinoma (NYCRM): A prospective, comparative phase II study.

Wenjia Zhu, Li Huo, Xiaoyuan Li, Yushi Zhang, Guoyang Zheng, Meixi Liu, Xinchun Yan; Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Peking Union Medical College Hospital, Beijing, China; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Peking Uion Medical College Hospital, Beijing, China

Background: ^{68}Ga-NY104 is a small-molecule PET agent selectively targeting carbonic anhydrase IX (CAIX), which is highly expressed on clear cell renal cell carcinoma (ccRCC). This phase II study aims to evaluate the diagnostic efficacy of ^{68}Ga-NY104 PET/CT in patients with metastatic clear cell renal cell carcinoma and compare it with ^{18}F-FDG PET/CT. **Methods:** Patients with metastatic ccRCC were prospectively recruited in this study (ClinicalTrials.gov: NCT05879471). All participants underwent ^{68}Ga-NY104 and ^{18}F-FDG PET/CT within one week. Tyrosine kinase inhibitors were stopped at least one week before the study. Any lesion that can be detected on either PET or CT is included for further analysis. The number and uptake of lesions were recorded. The diagnostic efficacy was determined at lesion level and region level based on a comprehensive reference standard protocol. **Results:** Forty-four patients (mean age, 59.6 ± 10.7) were recruited, including 40 men and 4 women. A total of 677 lesions in 172 regions were identified, of which 568 lesions and 128 regions were considered positive for ccRCC based on reference standard. The lesion-level sensitivity and specificity of ^{68}Ga-NY104 PET/CT to detect ccRCC lesion are 96.6% (95% CI, 95.2% - 98.1%) and 99.1% (95% CI, 97.3% - 100%), which is significantly higher than that of ^{18}F-FDG PET/CT (sensitivity, 77.8%, 95% CI, 74.4% - 81.2%, P < 0.001; specificity, 5.5%, 95% CI, 1.2% - 9.8%, P < 0.001). The region-level sensitivity and specificity of ^{68}Ga-NY104 PET are 98.4% (95% CI, 96.3% - 100%) and 97.7% (95% CI, 93.3% - 100%), which is also significantly higher than that of ^{18}F-FDG PET/CT (sensitivity, 82.0%, 95% CI, 75.4% - 88.7%, P < 0.001; specificity, 11.4%, 95% CI, 2.0% - 20.7%, P < 0.001).The SUVmax of ccRcc lesions (n = 568) were 12.6 ± 11.7 for ^{68}Ga-NY104 versus 7.5 ±10.5 for ^{18}F-FDG (P < 0.001). The TBR is also higher (15.7 ± 14.6 v.s. 4.8 ±5.5, P < 0.001). A significant SUVmax difference between ccRCC and non-ccRCC lesion was noted for ^{68}Ga-NY104 (12.6 ± 11.7 v.s. 1.2 ±1.0, P < 0.001), which is not true for ^{18}F-FDG (7.5 ±10.5 v.s. 6.5 ±3.5, P = 0.061). **Conclusions:** ^{68}Ga-NY104 PET/CT is a promising tool with high diagnostic efficacy in patients with metastatic ccRCC. It is better than ^{18}F-FDG PET/CT in both sensitivity and specificity. Clinical trial information: NCT05879471. Research Sponsor: National Natural Science Foundation of China; No. 82202218.

Diagnostic efficacy of ^{68}Ga-NY104 and ^{18}F-FDG PET/CT.

		Sensitivity	95% CI	Specificity	95% CI
Lesion-level (n=677)	68Ga-NY104	96.6%	95.2%-98.1%	99.1%	97.3%-100%
	18F-FDG	77.8%	74.4%-81.2%	5.5%	1.2%-9.8%
Region-level (n=172)	68Ga-NY104	98.4%	96.3%-100%	97.7%	93.3%-100%
	18F-FDG	82.0%	75.4%-88.7%	11.4%	2.0%-20.7%

4525 Poster Session

Anlotinib plus everolimus as first-line treatment for advanced non–clear cell renal cell carcinoma: 1 year updated results from UC-001, a single-center, single-arm, phase II trial.

Wen-Hao Xu, Hailiang Zhang, Dingwei Ye; Fudan University Shanghai Cancer Center, Shanghai, China; Department of Urology Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Cancer Hospital, Xuhui, Shanghai, China

Background: For patients (pts) with recurrent or stage IV non-clear cell renal cell carcinoma (nccRCC), the current guidelines recommend participation in clinical trials, or the use of tyrosine kinase inhibitors (TKIs), such as sunitinib, or mTOR inhibitors, such as everolimus. Anlotinib, a novel multi-target TKI, inhibits vascular endothelial growth factor receptors, fibroblast growth factor receptors, platelet-derived growth factor receptors, and c-kit. The ALTER-UC-001 study (NCT05124431) is a single-center, single-arm, phase II trial evaluating the efficacy and safety of anlotinib plus everolimus as first-line therapy in pts with advanced nccRCC. Data for 24 pts from Jan 2022 through Dec 2023 have been published in 2024 ASCO. Here, we present 1-year updated results. **Methods:** Eligible pts were those with advanced nccRCC and no prior systemic therapy for advanced disease, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Pts received anlotinib (12 mg orally once daily on days 1-14 of each 3-week cycle) and everolimus (5 mg orally once daily). The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Adverse events (AEs) were graded according to CTCAE v5.0. **Results:** Between January 2022 and December 2024, 32 pts were enrolled and received treatment. The median age was 56 years old (range: 20-79 years), and 46.9% of pts had papillary renal cell carcinoma (pRCC). Most pts (81.3%; 26/32) had a ECOG PS score of 1. At the data cutoff in December 2024, with a median follow-up of 11.9 months (95% CI 9.3-14.5), the ORR was 54.5% (95% CI 32.2-75.6), and the DCR was 100% (95% CI 84.6-100.0). The median PFS was 20.8 months (95% CI 12.0-29.6). Adverse events (AEs) of any grade occurred in 90.6% of pts, with the most common being proteinuria (40.6%), mucositis and hypertension (37.5%), and anemia, increased creatinine, elevated transaminases (18.8%), glutamic-pyruvic transaminase increased and hematuria (15.6%), and hypercholesterolemia (12.5%). Grade 3 treatment-related AEs (TRAEs) occurred in 15.6% of pts, with no treatment-related deaths. Treatment was suspended in 18.8% (6/32) and 12.5% (4/32) of pts due to TRAEs associated with everolimus and anlotinib, respectively. **Conclusions:** This study demonstrates that anlotinib combined with everolimus is an effective and tolerable first-line therapy for advanced nccRCC, achieving a high ORR and prolonged PFS, with manageable toxicity. These findings provide critical evidence supporting the use of this novel combination in nccRCC. Survival follow-up is ongoing, and further validation in larger, multi-center randomized trials is warranted. Clinical trial information: NCT05124431. Research Sponsor: None.

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, Yulu Peng, Deling Wang, Lijuan Jiang, Zhiling Zhang, Tingxuan Huang, Xi Zhong, Shengjie Guo, Hui Han, Wei Xiong, Xiuyu Cai, Fangjian Zhou; Department of Urology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China; 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 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 for 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; Sichuan Provincial People's Hospital, Chengdu, China; Department of General Internal Medicine, Sun Yat-Sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, 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 January 2024, 44 patients were enrolled with a median age of 46 years (range: 18-79), 13 (29.5%) had Fumarate deficient RCC, 10 (22.7%) had Papillary RCC, 9 (20.5%) had TFE3 rearranged RCC and 12 (27.3%) were unclassified. Among these participants, 44 patients were evaluable. 95.5% were IMDC intermediate- or poor-risk, 72.7% had prior nephrectomy and 97.7% had synchronous metastatic disease. ORR and DCR were 56.8% (95%CI 41.6-72.1) and 86.4% (95%CI 75.8-96.9) , respectively.≥1 and < 1 Combined Positive Score of PD-L1 expression were observed in 50% (22/44) and 38.6% (17/44) patients respectively, and the ORR was 72.7% (95%CI:52.2-92.9) and 41.2% (95%CI: 15.1-67.3) in the two groups. As of November 13, 2024, median follow-up time was 17.5m (95%CI 14.9-20.1). The median PFS was 13.6m (95%CI 8.6-18.6). Treatment-related grade 3/4 adverse events were observed in 22.7% (10/44) of the patients, encompassed proteinuria (3 patients, 7%), hyponatremia (2 patients, 4%), hypertension (1 patients, 2%), hepatic insufficiency (1 patients, 2%), fatigue(1 patients, 2%), rash (1 patients, 2%), decreased lymphocyte count (1 patients, 2%). 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. Clinical trial information: NCT05220267. Research Sponsor: None.

Investigation of tumor-associated macrophages (TAMs) and therapeutic resistance to immune checkpoint inhibitors (ICI) through single-cell analysis of renal cell carcinoma (RCC).

Soki Kashima, Rishabh Rout, Miya Hugaboom, Zhaochen Ye, Nicholas R. Schindler, Ro Malik, Anasuya Dighe, Maxine Sun, Gwo-Shu Mary Lee, Wenxin Xu, Sabina Signoretti, David Aaron Schoenfeld, Michael E. Hurwitz, Adebowale Adeniran, Peter Humphrey, Patrick Aloysius Kenney, Bradley Alexander McGregor, Rana R. McKay, Toni K. Choueiri, David A. Braun; Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Brigham and Women's Hospital, Boston, MA; Department of Medical Oncology, Yale School of Medicine, New Haven, CT; Department of Pathology, Yale School of Medicine, New Haven, CT; Department of Urology, Yale School of Medicine, New Haven, CT; University of California San Diego, San Diego, CA

Background: RCC is characterized by a tumor microenvironment (TME) enriched in TAMs, which suppress antitumor immunity in RCC. We conducted a comprehensive dissection of the TME using pre- and post-ICI treatment samples to identify specific TAM populations associated with ICI treatment resistance in RCC. **Methods:** A total of 70 tumor samples (58 clear cell and12 non-clear cell) were collected from 63 patients with advanced RCC, including 9 patients who were untreated, 10 patients who received non-ICI-based systemic therapies, and 44 patients who received ICI-based therapies. We excluded 17 patients with stable disease from the 44 patients and analyzed 29 samples prior to (n = 15) or after exposure to (n = 14) ICI-based therapies (mono-ICI, n = 11; ICI + ICI, n = 11; ICI + VEGFi, n = 6; other, n = 1) from 27 patients. We performed single-cell RNA-sequencing (scRNA-seq; 10x Genomics) on all 70 samples and established a comprehensive transcriptomics atlas of the RCC TME. We utilized non-negative matrix factorization (NMF) to identify interpretable gene programs for TAMs, comparing responders (R) (n = 18; complete or partial response) with non-responders (NR) (n = 11; progressive disease) to ICI-based therapies according to the best response based on RECIST. P-values from Wilcoxon signed rank test are reported. **Results:** 443,337 high-quality viable cells were annotated to lymphoid, myeloid, tumor, endothelial, or fibroblast compartments, capturing the RCC TME landscape. Among TAMs, we discovered underlying gene programs through NMF analysis, including "antigen presentation", "S100A8/9 inflammatory", "stress response", "C1Q/APOE/TREM2", "CD163/MRC1", "hypoxia", "interferon-stimulated genes", and "LILRB/SIGLEC10" programs. We identified that the LILRB/SIGLEC10-TAM subcluster was significantly increased in frequency in NR compared to R (p = 0.005). Notably, the significant increase in this program in NR was also observed in pre-treatment only samples (p = 0.014), suggesting a primary mechanism of resistance. This population was characterized by the expression of immune suppressive *LILRB1/2/3* genes, together with significant upregulation of the macrophage checkpoints *SIGLEC10* (a recently discovered "don't eat me signal" receptor) and *VISTA* (an immune checkpoint) compared to other TAMs ($p < 2.22E-16$, for each). **Conclusions:** Our comprehensive dissection of the RCC TME reveals an association between TAM population with an immunosuppressive gene program and ICI resistance through analysis of a large scRNA-seq dataset. This study provides immunobiological insights into potential therapeutic targets for next-generation combination therapy with ICIs, offering a foundation for understanding treatment evolution in RCC. Research Sponsor: Kohlberg Chair at Harvard Medical School and the Trust Family, Michael Brigham, Pan Mass Challenge and Loker Pinard Funds for Kidney Cancer Research.

Assessment of time-to-treatment-failure (TTF) as a surrogate endpoint for overall survival (OS) to immune checkpoint inhibitor (ICI) regimens in metastatic renal cell carcinoma (mRCC): Findings from an IMDC analysis.

Zachary Yochum, Renee Maria Saliby, Wanling Xie, Vivien Moritz, Connor Wells, Evan Ferrier, Martin Zarba, Hedyeh Ebrahimi, Cristina Suárez, Jose Manuel Ruiz-Morales, Rana R. McKay, Thomas Powles, Lori Wood, Aly-Khan A. Lalani, Sumanta Kumar Pal, Guillermo de Velasco, Kosuke Takemura, Neeraj Agarwal, Daniel Yick Chin Heng, Toni K. Choueiri; Yale Cancer Center, New Haven, CT; Dana-Farber Cancer Institute, Boston, MA; Yale Cancer Center, Yale School of Medicine, New Haven, CT; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Tom Baker Cancer Centre, Calgary, AB, Canada; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; City of Hope Comprehensive Cancer Center, Duarte, CA; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Hospital Medica Sur, Toriello Guerra, DF, Mexico; Moores Cancer Center, University of California San Diego, La Jolla, CA; Barts Cancer Centre, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, London, United Kingdom; Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada; Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA; Hospital 12 de Octubre, Madrid, Spain; Department of Genitourinary Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: In Phase III trials for mRCC, OS is a gold standard primary endpoint. However, for ICI-based regimens, this requires extended follow-up times, resulting in higher costs and delayed drug approvals. Identification of surrogate or intermediate endpoints for OS would be beneficial in addressing these challenges. In the current study, we investigated 6-month TTF as a potential intermediate endpoint (IE) for OS in mRCC. **Methods:** We included all patients from the International mRCC Database Consortium (IMDC) who received ICI-based regimens from 2013 to 2023. TTF was defined from ICI start until drug cessation or death or censored at date of last follow-up. The cohort was divided into 10 equal sub-cohorts based on the decile disease risk scores, calculated using multivariable Cox regression for OS, considering all relevant covariates (IMDC risk groups, presence of bone, brain, or liver metastases, histology, age, prior nephrectomy, ICI type, and year of ICI initiation). For these sub-cohorts, we used Kaplan-Meier methods to determine 18-month OS and event-free rates for 6, 9, and 12-month TTF. We then performed linear regression of stratum-specific 18-month OS against stratum-specific 6-month (and 9- and 12-month) TTF. In the landmark analysis, OS was calculated starting at 6 months after therapy initiation, excluding patients who died or had follow-up of less than 6 months. **Results:** The IMDC cohort consisted of 1667 patients with a median age of 63 years and 83% had clear cell histology. Median follow-up was 15.4 months (IQR: 7.1-28.6). Across the 10 sub-cohorts, 6-month TTF accounted for 76% of the variance in 18-month OS (R^2= 0.76, 95% CI: 0.26-0.87). Similar patterns were seen for 9 (R^2= 0.65, 95% CI: 0.11-0.81) and 12-month TTF (R^2= 0.64, 95% CI: 0.09-0.80). In the 6-month landmark analysis (evaluable n = 1255), mRCC patients experiencing treatment failure at 6 months had an 18-month OS (i.e. 12 months after the landmark time) rate of 68% (95% CI: 63%-72%), compared to 92% (95% CI: 90%-94%) for those without treatment failure (adjusted HR: 2.74, 95% CI 2.15-3.49). **Conclusions:** 6-month TTF was predictive of 18-month OS in mRCC patients. These findings suggest that 6-month TTF may be a promising intermediate endpoint for OS and provides supportive evidence of future validation in prospective studies. Research Sponsor: None.

Phase 1 results of Oncobax-AK in combination with ipilimumab/nivolumab in advanced clear cell renal cell carcinoma (ccRCC; NCT05865730).

Lisa Derosa, Philippe Barthelemy, Brigitte Laguerre, Fabrice Barlesi, Bernard Escudier, Laurence Zitvogel, Laurence Albiges; Gustave Roussy Cancer Campus (GRCC), ClinicObiome, Villejuif, France; Hôpitaux Universitaires de Strasbourg, Institut de Cancérologie Strasbourg Europe, Strasbourg, France; Centre Eugene Marquis, Rennes, France; Gustave Roussy and Paris Saclay University, Villejuif, France; Gustave Roussy, Villejuif, France; Institut Gustave Roussy, Villejuif, France; Gustave Roussy, Paris Saclay University, Paris, France

Background: Patients with advanced solid tumors who respond to immunotherapy are more likely to have *Akkermansia spp (Akk)* in their stools, whereas its absence (45%) is associated with worse outcome, regardless of other prognostic factors. Here, we report the safety and efficacy findings from a Phase I trial evaluating Oncobax-AK live biotherapeutics in combination with nivolumab/ipilimumab in intermediate- and poor-risk IMDC ccRCC patients who tested negative for stool *Akk*. We report first results of cohort 1. **Methods:** Intermediate- and poor-risk IMDC advanced ccRCC patients were screened across 4 centers in France for *Akk* using a qPCR stool test designed to detect specific *Akk* strains (SGB9226/SGB9228). Patients who tested negative for stool *Akk* received either 1X (cohort 1) or 6X oral capsules (cohort 2) of Oncobax-AK (a specific strain of SGB9228, p2261) for one week as monotherapy, followed by a combination treatment with nivolumab/ipilimumab administered continuously until progression in cohorts 1 and 2, respectively. The primary endpoints were safety, pharmacodynamics of Oncobax-AK, and overall response rate (ORR) according to RECIST 1.1. Blood and stool samples were collected at multiple time points for multi-omics analyses. **Results:** Among the 29 patients screened for *Akk*, 11 (38%) did not harbor gut *Akk* and were eligible. Two patients declined to continue. Ultimately, 9 patients (8 intermediate and 1 poor IMDC risk group) were enrolled in cohort 1, with a median age of 57 years (n = 9: 1 female and 8 males). No serious adverse events related to Oncobax-AK was observed. Only one patient experienced a serious immunotherapy-related adverse event that led to treatment withdrawal. After a median follow-up of 14.9 months, all patients are still alive, with 4 showing a partial response (PR) for more than 6 months (including 2 patients with ongoing PR for over 15 months, continuing the intervention). One patient had stable disease (SD), 3 had progressive disease (PD), and 1 was not evaluable (NE). Among evaluable patients, the ORR was 50%. Multi-omics analyses revealed that Oncobax-AK remains detectable over time and induced changes in the microbiome, leaky gut markers, and immune and metabolite profiles. These changes suggest potential pharmacodynamic biomarkers, reflecting the biological effects of Oncobax-AK. **Conclusions:** This is the first trial targeting patients lacking *Akkermansia spp.* in their stools. Oncobax-AK, combined with Ipilimuab/Nivolumab in intermediate- and poor-risk IMDC ccRCC, appears safe and may modulate gut microbiota, inflammation, metabolites, and immune profiles. This potentially mimics a responder's profile and leads to clinical and radiological benefits in some patients. Based on these promising results, enrollment in cohort 2 (6X) is ongoing and has now been expanded to include non-small cell lung cancer patients. Clinical trial information: NCT05865730. Research Sponsor: None.

Co-expression network-based analysis of gene programs contributing to immune checkpoint inhibitor (ICI) resistance in renal cell carcinoma (RCC).

Ro Malik, Rishabh Rout, Soki Kashima, Eddy Saad, Harry Kane, Valisha Shah, Miya Hugaboom, Zhaochen Ye, Nicholas R. Schindler, Anasuya Dighe, Maxine Sun, Gwo-Shu Mary Lee, Wenxin Xu, Sabina Signoretti, Bradley Alexander McGregor, Rana R. McKay, Michael B. Atkins, Eliezer Mendel Van Allen, Toni K. Choueiri, David A. Braun; Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; Dana-Farber Cancer Institute, Boston, MA; Yale School of Medicine, New Haven, CT; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Department of Pathology, Brigham and Women's Hospital, Boston, MA; University of California San Diego, San Diego, CA; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: There is an unmet need to characterize molecular drivers of resistance to ICIs in the RCC tumor microenvironment, especially in cell-type-specific contexts. To address this, we identified coherent gene programs in each cell type using scRNA-seq data to uncover an immune cell phenotype associated with ICI resistance. **Methods:** We performed per-cell-type weighted coexpression network analysis on scRNA-seq data of 443,337 cells from 70 RCC tumor samples, mostly from patients (pts) who received ICI (S. Kashima, ASCO, 2024), to construct mutually co-expressed gene sets (modules) and their cell-level expression. We compared module expression scores between responders (R, complete or partial response) and non-responders (NR, progressive disease) with the Wilcoxon rank-sum test plus FDR correction, and ran tests with permuted labels to rule out statistical artifacts. For validation, we performed this analysis on another scRNA-seq cohort from a phase II trial (HCRN GU16-260; NCT03117309), and further, we used CoxPH survival analysis on module signature scores computed by GSVA to assess the prognostic role of module expression in bulk RNA-seq samples from the IMmotion 150, CheckMate 009/010/025, and Javelin 101 trials, after stratifying them into immune-high (top 50%) and immune-low (bottom 50%) groups according to CIBERSORTx-inferred total immune infiltration. **Results:** Analysis of scRNA-seq (two independent datasets) from ICI-treated RCC tumors revealed a module of robustly co-expressed ribosomal and translation-associated genes that was significantly upregulated in NR in immune cells (but not tumor or stromal cells), including macrophages, CD4+ and CD8+ T, NK, and B cells (p-values ranging from 1e-20 to 1e-200). Analysis of an independent scRNA-seq cohort (HCRN GU16-260) also yielded a module of mutually co-expressed ribosomal proteins only in immune cells that was upregulated in NR (immune $p < 1e-20$, non-immune $p > .05$). Finally, validation in large-scale bulk RNA-seq data from clinical trials shows that for patients receiving any ICI-based therapy (nivolumab, avelumab + axitinib, or atezolizumab +/- bevacizumab), module signature scores were significantly associated with worse PFS only in the CoxPH analysis of immune-high samples (HR = 1.65, 95% CI, 1.18–2.3, $p < .005$), while immune-low samples showed no effect (HR = 0.93, 95% CI 0.71–1.25, $p > .5$), concordant with findings from the scRNA-seq analysis. Those receiving a TKI only (sunitinib) exhibited no association, regardless of immune infiltration. **Conclusions:** Though individual ribosomal proteins have been found to be prognostic for RCC, a cell-type-specific module-level analysis elucidated a link between a coherent translation program in immune cells and resistance and poor PFS for pts receiving ICI specifically, contributing to a model of ICI-resistant molecular phenotypes in RCC. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 1R37CA279822.

Frailty assessment in patients with advanced/metastatic renal cell carcinoma using routine data collected during treatment with tyrosine kinase inhibitors in the STAR trial.

Sophie Trotter, Kara-Louise Royle, Cat Handforth, Lynda Wyld, Janet Brown; Weston Park Cancer Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom; School of Medicine and Population Health, University of Sheffield, Sheffield, United Kingdom

Background: The STAR trial (ISRCTN06473203) was a phase 2/3 randomised controlled non-inferiority trial (N=920) which assessed whether treatment breaks from tyrosine kinase inhibitors (TKIs, oral sunitinib/pazopanib) could be safely used in locally advanced/metastatic renal cell carcinoma (RCC). We aimed to determine if it was possible to obtain a frailty index (FI) which could be linked to toxicity and clinical outcomes from routinely collected large trial data, using the STAR trial as an example. **Methods:** We developed the FI using Rockwood's accumulation of deficits methodology. STAR data was initially searched for variables measuring baseline health problems and functional limitations. Variables were excluded if there was a significant proportion of missing values (>10%); if too rare or too common (<1%, >80%); or if significantly correlated with another variable (r>0.95). Variables were coded from 0 (no deficit) to 1 (full deficit); these were summed then divided by the number of variables assessed to give the FI. Frailty thresholds were adopted in line with the literature: Not Frail (FI≤0.08); Pre-Frail (FI 0.08-0.24); Frail (FI≥0.25). **Results:** Of 57 variables screened, 35 variables remained for inclusion in the FI. 50 participants missing >20% of FI variables were excluded, leaving n=870. FI scores ranged from 0 to 0.43 (median 0.15, IQR 0.10-0.22). Kaplan-Meier survival analysis showed a statistically significant difference by FI for overall survival (OS) (FI≥0.25: HR 2.48, p<0.001, 95% CI 1.89-3.26). In multivariate Cox proportional hazards regression, FI remained a statistically significant risk factor for OS (HR 1.41, P=0.047, 95% CI 1.00-1.99); other statistically significant variables included age group, sites of metastatic disease, IMDC and MOTZER scores. Toxicity was assessed over the first 6 months, while all participants were treated with continuous TKIs. The most common severe toxicities (G3+) were hypertension (200/870), hepatobiliary disorders (97/870) and fatigue (63/870). Time free of severe toxicity was statistically significantly shorter for frail participants. **Conclusions:** Amongst STAR trial participants with advanced/metastatic RCC treated with TKIs, frailty was a statistically significant risk factor for poorer survival and for shorter time to severe toxicity. It is noted that the eligibility criteria for STAR included a baseline PS of ECOG 0-1 which will have excluded many frailer patients. This data shows that it is feasible to use routinely collected trial data to create a clinically meaningful FI and this approach could be applied to other trial datasets. Clinical trial information: ISRCTN06473203. Research Sponsor: UK National Institute for Health and Care Research (NIHR).

Toxicity-free survival, by frailty group.

Toxicity	FI group	HR	p-value	95% CI
Severe toxicity (G3+)	Intermediate	1.00	0.960	0.83-1.21
	Frail	1.28	0.025	1.03-1.59
All toxicity (G1+)	Intermediate	1.11	0.031	1.01-1.22
	Frail	1.08	0.201	0.96-1.20

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification and regression tree analysis to characterize objective response rates (ORR) in metastatic renal cell carcinoma (mRCC).

Martin Zarba, Dylan O'Sullivan, David Maj, Winson Y. Cheung, Lisa Ludwig, Connor Wells, Evan Ferrier, Razane El Hajj Chehade, Frede Donskov, Marc Eid, Sumanta Kumar Pal, Benoit Beuselinck, Rana R. McKay, Lori Wood, Jae Lyun Lee, Cristina Suárez, Kosuke Takemura, Ignacio Duran, Toni K. Choueiri, Daniel Yick Chin Heng; Arthur J.E. Child Comprehensive Cancer Centre, Calgary, AB, Canada; University of Calgary, Calgary, AB, Canada; IPSEN, Edmonton, AB, Canada; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Dana-Farber Cancer Institute, Boston, MA; University Hospital of Southern Denmark, Esbjerg, Denmark; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA; UZ Leuven, Leuven, Belgium; UC San Diego School of Medicine, San Diego, CA; Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Department of Genitourinary Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Hospital Universitario Marqués de Valdecilla, IDIVAL Santander, Santander, Spain; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Arthur JE Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: Therapies for mRCC have evolved significantly, making treatment decisions more complex. We used machine learning (ML) to identify whether this could help identify subgroups of patients who have a high probability of response. **Methods:** Patients from IMDC were identified and a ML classification and regression tree analysis was conducted, in which we grew a complex tree up to a depth of 30 with a minimum node split size of 2 with no constraints on the cost-complexity parameter. The resulting tree was pruned according to the cost-complexity parameter that minimized the leave one out cross-validated error rate and had a minimum bucket size of 25 patients. **Results:** 2,549 patients were included, 73.2% male, 13.5% non-clear cell histology, 70.3% nephrectomy, and 19.4%, 54.2%, and 26.4% had favorable, intermediate and poor IMDC risk respectively. 1L treatment regimens consisted of VEGF inhibitors (51.5%), IO-IO combinations (32.3%), and IO-TKI combinations (16.2%). The ORR was 36.0% overall, with 29.6% for VEGF inhibitors, 39.1% for IO-IO, and 50.2% for IO-TKI combinations. ML identified 5 hierarchal variables —therapy type, prior nephrectomy (PN), lung metastasis (LM), other metastases, and age— that divided patients into 7 different categories with different response probabilities (see Table). VEGF therapy showed the poorest response, with no additional variables able to predict response. The best ORR was observed in patients treated with IO-TKI and PN; and in those treated with IO-IO, PN, and only lung metastasis. Factors associated with poorer responses included non-clear cell histology, older age, bone and liver metastases, poor performance status, elevated neutrophils, and poor IMDC risk score. **Conclusions:** This large-scale ML analysis identified five key clinical variables that predict treatment response in mRCC, with treatment type emerging as the primary determinant. These results suggest that treatment selection for mRCC could potentially be optimized by considering these hierarchical variables, though further validation is needed. Research Sponsor: None.

ML analysis results: Groups of patients and associated outcomes.

Risk Groups	N (%)	ORR (%)	Odd Ratio	TTNT	18-month survival
1) VEGF	1313 (51.5)	29.6	Ref.	9.4 (8.6-10.3)	0.62 (0.59-0.65)
2) IO-IO or IO-TKI and no PN	443 (17.4)	35.0	1.28 (1.02-1.60)	10.2 (8.8-11.3)	0.59 (0.55-0.65)
3) IO-IO and PN					
a) No LM	137 (5.4)	29.2	0.98 (0.66-1.43)	17.2 (10.6-30.1)	0.85 (0.78-0.92)
b) LM and other met	267 (10.5)	43.8	1.87 (1.42-2.44)	13.0 (10.1-20.5)	0.78 (0.72-0.83)
c) Only LM	85 (3.3)	60.0	3.56 (2.28-5.63)	39.2 (14.4-NA)	0.93 (0.87-0.99)
4)IO-TKI and PN					
a) Age 70+	78 (3.2)	43.6	1.84 (1.15-2.91)	35.7 (19.8-NA)	0.80 (0.71-0.91)
b) Age < 70	226 (8.9)	58.4	3.34 (2.50-4.47)	24.7 (22.4-36.4)	0.88 (0.84-0.93)
Overall	2549	36.0		11.5 (10.7-12.2)	0.68 (0.67-0.70)

Early detection of renal cell carcinoma: A novel cfDNA fragmentomics-based liquid biopsy assay.

Yulu Peng, Tingxuan Huang, Zhaohui Zhou, Hao Zhang, Wanxiangfu Tang, Xiuxiu Xu, Dongqin Zhu, Ruowei Yang, Haimeng Tang, Hua Bao, Xue Wu, Hui Han, Zhiling Zhang, Liru He, Pei Dong, Wensu Wei; 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, Sun Yat-Sen University Cancer Center, Guangzhou, China; Nanjing Geneseeq Technology Inc., Nanjing, China; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, 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: Renal cell carcinoma (RCC) is a leading cause of cancer-related mortality, with a rapidly rising global incidence. Early detection greatly improves the outcomes of RCC, yet current diagnostic methods have limitations in sensitivity, specificity, and accessibility. This study develops and evaluates a cfDNA fragmentomics-based liquid biopsy integrated with machine learning as a non-invasive and scalable tool for RCC early detection. **Methods:** This case-control cohort study recruited 442 participants (223 RCC patients and 219 non-cancer controls, including healthy individuals and those with benign renal conditions) at a single cancer referral center from December 2021 to December 2023. Plasma-derived cfDNA underwent low-pass WGS (5X coverage), and three fragmentomics features—copy number variation (CNV), fragment size ratio (FSR), and nucleosome footprint (NFP)—were extracted. A stacked ensemble machine learning model was trained on 280 participants and validated on 162 independent participants. Performance was assessed using area under the curve (AUC), sensitivity, and specificity. **Results:** The ensemble model achieved an AUC of 0.9656 in the validation cohort, with sensitivity and specificity of 90.5% and 93.8%, respectively. Stratified analyses demonstrated consistent performance across RCC stages, histological subtypes, and Fuhrman grades, with sensitivities of 87.8% for Stage I RCC and 100% for Stage IV RCC. Additionally, the model effectively differentiated malignant RCC from benign renal conditions, further validating its clinical utility. Stability evaluations confirmed the model's robustness across diverse sample types, storage conditions, and processing scenarios, underscoring its potential applicability in routine clinical practice. **Conclusions:** This cfDNA fragmentomics-based liquid biopsy represents a highly sensitive, specific, and non-invasive approach for the early detection of RCC. Its robust performance across diverse clinical scenarios highlights its potential to enhance current RCC diagnostic workflows, facilitate timely interventions, and improve patient outcomes. Future integration of this method into clinical practice could address critical gaps in RCC management, providing substantial benefits in early detection and personalized care. Research Sponsor: National Natural Science Foundation of China; Science and Technology Projects in Guangzhou; The China National Postdoctoral Program for Innovative Talents.

4535 Poster Session

Efficacy and safety of neoadjuvant toripalimab plus axitinib in renal cell carcinoma with tumor thrombus: A combined analysis of two phase II trials.

Liangyou Gu, Cheng Peng, Zhuolong Wu, Yaohui Wang, Qiyang Liang, Dongxing Wang, Houming Zhao, Baojun Wang, Qingbo Huang, Xu Zhang, Xin Ma, Jiwei Huang; Chinese PLA General Hospital, Beijing, China; Department of Urology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Tumor thrombectomy for renal cell carcinoma (RCC) with tumor thrombus (TT) is associated with high morbidity and mortality. Two trials have demonstrated the efficacy and safety of neoadjuvant toripalimab plus axitinib in patients with TT. Here, we present the pooled analysis results. **Methods:** These two phase II trials (NEOTAX and NCT04118855) shared similar target populations. Patients with clear cell RCC (ccRCC) and TT received up to 12 weeks of toripalimab plus axitinib before surgery. The primary endpoint was the downstaging rate of TT based on the Mayo classification. For level 0 thrombus, the downstaging defined as: for right RCC, the proximal end of TT retracted from the main renal vein to branches of the renal vein; for left RCC, the superior mesenteric artery (SMA) was an anatomical landmark, the TT retracted from lateral to the abdominal aorta to the level of SMA or from the main renal vein lateral to SMA or the branches of the renal vein. Secondary endpoints included response rate, change in thrombus length, surgical morbidity, progression-free survival (PFS), overall survival (OS), and safety. **Results:** A total of 40 patients were enrolled, 4 (10%), 4 (10%), 14 (35%), 7 (17.5%), 11 (27.5%) patients had level 0, I, II, III, IV tumor thrombus, respectively. After 12 weeks treatment, 45.0% (18/40) patients experienced a reduction in TT level, one patient (2.5%) had an increase in Mayo level. Thirty-six (90%) patients exhibited shrinkage in TT length, with a median reduction of 1.9 cm (IQR: 0.9 to 3.7 cm). According to the RECIST criteria, the objective response rate and disease control rate of overall tumor was 37.5% and 97.5%. In total, 35 patients underwent radical nephrectomy with IVC thrombectomy, including 16 open, 2 laparoscopic and 17 robotic. No patient had a surgery delay due to treatment-related adverse events (TRAEs). 54.3%(19/35) patients experienced changes in surgical strategy compared with planned surgery. Median operation time was 300 min (IQR: 180-420 min). Median estimated blood loss was 700 ml (IQR: 300-1800 ml). The postoperative complication rate was 60% (21/35), including three (8.6%) major complications and one (2.9%) postoperative death. The most common TRAEs included hypertension (35.0%), proteinuria (35.0%), fatigue (27.5%), and diarrhea (22.5%). Grade ≥3 adverse events were reported in 27.5% (11/40) of patients, no patients experienced Grade 4 or 5 TRAEs. With a median follow-up of 32.2 (IQR: 27.0-35.5) months, the median PFS and OS were not reached. The estimated PFS rate at 1 year was 87.5% (95% CI, 72.4% to 95.3%). The PFS (P = 0.20) and OS (P = 0.44) were similar between responders (partial response) and non-responders (stable disease or progressive disease). **Conclusions:** Toripalimab in combination with axitinib downstages TT level in a significant proportion of patients leading to simplification in the procedure of surgery. Clinical trial information: NCT04118855. Research Sponsor: None.

First-line benmelstobart plus anlotinib versus sunitinib in advanced renal cell carcinoma: Subgroup analysis from the phase 3 ETER100 trial.

Xinan Sheng, Pengfei Shen, Zengjun Wang, Xiubao Ren, Yuan Li, Shusuan Jiang, Gang Li, Yu Zeng, Weijun Qin, Jin Wu, Peng Chen, Fangjian Zhou, HongQian Guo, Zhigang Ji, Yongquan Wang, Zhisong He, Benkang Shi, Lian Liu, Aiping Zhou, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Department of Urology and Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Chongqing university cancer hospital, Chongqing, China; Department of Urology, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Hunan Cancer Hospital, Hunan, China; The Second Hospital of Tianjin Medical University, Tianjin, China; Urology Department of Liaoning Cancer Hospital & Institute, Shenyang, -, China; Xijing Hospital of Air Force Military Medical University, Xi'an, China; Affiliated Cancer Hospital of Harbin Medical University, Harbin, China; Affiliated Tumor Hospital of Xinjiang Medical University, Urumqi, Xinjiang, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China; Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, Nanjing, China; Department of Medical Oncology, Peking Union Medical College Hospital, Beijing, China; Department of Urology, Southwest Hospital, Army Medical University, Chongqing, China; Peking University First Hospital, Beijing, China; Department of Urology, Qilu Hospital of Shandong University, Jinan, China; Department of Chemotherapy, Cancer Center, Qilu Hospital of Shandong University, Jinan, China; Tumor Hospital, Chinese Academy of Medical Sciences, Beijing, China; Beijing Cancer Center, Beijing, China

Background: Dual immune checkpoint inhibitors (ICIs) or ICIs plus VEGF-directed therapies, have been approved as first-line treatment in patients (pts) with advanced renal cell carcinoma (RCC). The phase 3 ETER100 trial showed that benmelstobart (PD-L1 blockade) plus anlotinib improved the progression-free survival (PFS) (19.0 months 9.8 months) and objective response rate (ORR) (71.6% vs 25.1%) of advanced clear cell RCC (ccRCC) pts significantly. Pts with factors, such as intermediate-poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk, liver metastasis, or bone metastasis were considered to have a poor prognosis. Here we report PFS and ORR in clinically relevant subgroups. **Methods:** ETER100 (NCT04523272) was a multicentre, randomised, open-label, controlled phase 3 trial conducted at 37 sites in China. Eligible patients were randomly assigned in a 1:1 ratio using stratified block randomisation to receive benmelstobart plus anlotinib or sunitinib. Randomisation was stratified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk (favourable [score of 0], intermediate [score of 1-2], or poor risk [score of 3-6]). PFS analyses of clinically relevant subgroups were assessed using Kaplan-Meier method and the 95% CIs of response rate were calculated with the Clopper-Pearson method. **Results:** Overall, 527 pts received the trial treatments (264 in the benmelstobart-anlotinib group and 263 in the sunitinib group) and were evaluated for efficacy. A total of 454 (86%) pts had intermediate-poor IMDC risk, 62 (12%) pts had liver metastasis and 111(21%) had bone metastasis. Data cutoff for the interim analysis occurred on January 31, 2024. The median follow-up was 22.8 months. Benmelstobart plus anlotinib significantly improved PFS of subgroups with intermediate-poor IMDC risk (17.0 months [95% CI 14.0-20.1] vs 9.7 months [8.0-11.3], HR 0.55, 95% CI 0.43-0.72; $p < 0.0001$), liver metastasis (11.9 months [95% CI 5.8-NE] vs 5.4 months [1.5-6.7], HR 0.44, 95% CI 0.23-0.85; $p < 0.0121$), or bone metastasis (19.5 months [95% CI 16.5-27.2] vs 8.3 months [4.2-19.8], HR 0.52, 95% CI 0.30-0.89; $p < 0.0154$). ORR of benmelstobart-anlotinib group was significantly higher in the subgroups with intermediate-poor IMDC risk (70.0% [95%CI, 63.6- 75.9] vs 21.6% [16.4-27.5]), liver metastasis (60.0% [95%CI, 42.1-76.1] vs 7.4% [0.9-24.3]) and bone metastasis (63.2% [95%CI, 49.3-75.6] vs 16.7% [7.9-29.3]). **Conclusions:** The RCC pts with a poor prognosis such as intermediate-poor IMDC risk, liver metastasis and bone metastasis could significantly benefit from benmelstobart plus anlotinib. Clinical trial information: NCT04523272. Research Sponsor: None.

4537 Poster Session

Ongoing phase 1/2 trial of the hematopoietic progenitor kinase 1 (HPK1) inhibitor NDI-101150 as monotherapy or in combination with pembrolizumab: Clinical safety and efficacy update in clear cell renal cell carcinoma (ccRCC).

David A. Braun, Kurt C. Demel, Marcus Smith Noel, Hamid Emamekhoo, Julio Antonio Peguero, Rama Balaraman, Ryan H. Moy, Martin Gutierrez, Sunil Sharma, Arif Hussain, Joanna Haas, Daria Chabas, Sue Dasen, Xinyan Zhang, Scott R. Daigle, Ginell Elliott, Sritama Nath, Pavan Kumar, Anita Scheuber, David Sommerhalder; Center of Molecular and Cellular Oncology, Yale University, New Haven, CT; Cancer Research Center, HealthPartners Institute, Saint Paul, MN; Georgetown University, Washington, DC; University of Wisconsin-Madison, Madison, WI; Oncology Consultants, Houston, TX; Ocala Oncology, Florida Cancer Affiliates, Ocala, FL; Columbia University Irving Medical Center – Herbet Irving Pavillion, New York, NY; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Honor Health Research Institute, Scottsdale, AZ; University of Maryland Medical Center, Greenebaum Comprehensive Cancer Center, Baltimore, MD; Nimbus Therapeutics, Boston, MA; Nimbus Therapeutics (Nimbus Discovery Inc.) on Behalf of Nimbus Saturn Inc., Boston, MA; NEXT Oncology, San Antonio, TX

Background: NDI-101150 is a potent and selective oral inhibitor of HPK1, a serine/threonine kinase that acts as a negative regulator of immune cell function. Pre-clinically, NDI-101150 can enhance immune cell function, leading to potent anti-tumor immunity. **Methods:** NDI-101150 is currently being investigated in a first-in-human, multi-center, open-label, phase 1/2 trial (NCT05128487) in patients with advanced solid tumors, as a monotherapy (50–200 mg once daily [QD]) or in combination with pembrolizumab (50–100 mg QD NDI-101150 + 200 mg Q3W pembrolizumab). **Results:** As of 20 November 2024, 106 patients were dosed [NDI-101150 monotherapy (n = 94) or NDI-101150 + pembrolizumab (n = 12)]. The tumor types were RCC (n = 38), NSCLC (n = 17), gastric/GEJ (n = 12), and other solid tumors (n = 39). We report here updated safety data in all patients from monotherapy and combination arms (n = 106), and efficacy data in patients with ccRCC (n = 29) receiving NDI-101150 monotherapy. NDI-101150 monotherapy was generally well tolerated, with 150 mg identified as the maximum tolerated dose. The most common treatment-related adverse events (TRAEs) of any grade were nausea (39%), diarrhea (35%), vomiting (29%), fatigue (27%), and anemia (11%). Grade ≥3 TRAEs occurred in 13 (14%) patients, of which only 1 (1%) patient experienced a grade 4 TRAE. The safety profile was comparable in the combination cohort, with 2 (17%) patients experiencing Grade ≥3 TRAE. 20 of the 29 ccRCC patients who received 50, 100, 140, or 150 mg of NDI-101150 monotherapy were response-evaluable. The objective response rate was 15.0% [CR, n = 1 and PR, n = 2]. Clinical benefit rate (CR + PR + SD ≥6 months) was 25%, which includes 2 patients who experienced durable SD for ~9 months and ~25 months. The disease control rate (CR+PR+SD) was 60%. The ccRCC patients had received a median of 2 (1–9) lines of prior therapy. A nearly dose-proportional increase in NDI-101150 exposure was observed at day 1, with steady state achieved by day 15. At all doses tested, steady state exposures inhibited the pharmacodynamic biomarker pSLP76 by > 50% and for a period consistent with preclinical efficacy predictions. To demonstrate proof of biology, a custom 12-plex immunofluorescence panel and the GeoMx whole transcriptomic assay were utilized. By day 28, on-treatment tumor biopsy samples showed immune activation when compared to pre-treatment samples, including an increased infiltration of activated CD8+ T-cells and dendritic cells. **Conclusions:** NDI-101150 continues to demonstrate an acceptable safety profile and encouraging antitumor activity in patients with ccRCC, supporting continued clinical development of NDI-101150 as monotherapy and in combination with other agents as a promising next-generation immunotherapy oral small molecule. Clinical trial information: NCT05128487. Research Sponsor: Nimbus Therapeutics.

Genomic and proteomic predictors of sites of metastases in renal cell carcinoma.

Clara Steiner, Eddy Saad, Marc Machaalani, Renee Maria Saliby, Marc Eid, Karl Semaan, Emre Yekeduz, Liliana Ascione, Jack T. Horst, Jasmine Lee, Noa Phillips, Rachel Trowbridge, Gwo-Shu Mary Lee, Michal Harel, Adam P. Dicker, Bradley Alexander McGregor, David A. Braun, Rana R. McKay, Toni K. Choueiri, Wenxin Xu; Dana-Farber Cancer Institute, Boston, MA; Center of Molecular and Cellular Oncology, Yale University, New Haven, CT; Oncohost Ltd, Binyamina, Israel; Thomas Jefferson University, Philadelphia, PA; University of California, San Diego, San Diego, CA

Background: Among patients with renal cell carcinoma (RCC), the most common sites of metastasis are lung, lymph nodes, and bone. While some sites of metastases are associated with better cancer-specific outcomes than others, the underlying biology of metastatic organ tropism is not well understood. We performed genomic and proteomic analyses to investigate the biological underpinnings of different metastatic sites in RCC. **Methods:** Institutional cohorts of patients with metastatic RCC from the Dana-Farber Cancer Institute (DFCI) were analyzed using a next-generation tumor somatic mutation assay (n = 633) and with a highly multiplexed plasma proteomics assay (n = 258). Data were clinically annotated for sites of RCC metastasis. Genomic analyses were performed using a two-sided Fisher's exact test on the cBioPortal platform at DFCI with pairwise comparison of patients with versus without metastases to lung, liver, brain, bone, adrenal, and lymph nodes. The Benjamini-Hochberg method was applied for FDR-adjusted q-values. Exploratory proteomic analyses were performed using logistic regression for each metastatic site with multivariate adjustment for other sites of metastasis. For each metastatic site, the top five associated proteins were selected to build a multivariate model to predict the presence of each metastatic site. Bootstrapping with R = 1,000 was employed for the assessment of model performance. **Results:** Tumor genomic alterations in *SETD2* (q-value = 0.004) and *CDKN2A* (q-value = 0.04) were associated with lung and lymph node metastases, respectively. Logistic regression analyses of proteomic data were used to identify circulating proteins with the strongest associations with the sites of metastases. For instance, circulating collagen alpha-1(IX) chain (CO91A) and relaxin receptor 1 (RXFP1) were the top circulating proteins associated with bone metastases, while GGT2 and tenascin were associated with liver metastases and matrilysin (MMP-7) was associated with lymph node metastases. Multivariate models using the top five proteins to predict the presence of each metastatic site demonstrated bootstrapped C-statistics from 0.72 to 0.80 for lymph nodes, lung, adrenal, brain, liver, and bone, respectively. **Conclusions:** We identified genomic and proteomic predictors of organ-tropic metastases in RCC. Next, we will validate these findings in independent external cohorts. Research Sponsor: None.

Analysis of phase II study of cabozantinib (Cabo) with nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma with divergent histologies (RCCdh).

Bradley Alexander McGregor, Morgan Paul, Wanling Xie, Wenxin Xu, Stephanie A. Berg, Mehmet Asim Bilen, David A. Braun, Tian Zhang, Rana R. McKay, Hans J. Hammers, David F. McDermott, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Winship Cancer Institute of Emory University, Atlanta, GA; Center of Molecular and Cellular Oncology, Yale University, New Haven, CT; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; University of California San Diego, San Diego, CA; Beth Israel Deaconess Medical Center, Boston, MA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: We previously reported on treatment intensification with the combination of Cabo/Nivo/Ipi in 39 patients (pts) with metastatic RCCdh in a multi-center single arm phase II trial with a starting cabozantinib dose of 40 mg/day (d). Clinical utility was limited with an objective response rate (ORR) of 21% and significant treatment related adverse events (TrAEs) (77% ≥Grade 3 TrAEs). Therefore, we explored the safety and potential efficacy by using a lower starting dose of cabozantinib of 20 mg/d (NCT04413123). **Methods:** Eligible pts had metastatic RCCdh with ECOG performance status of 0-1 and may have received one line of prior therapy excluding immunotherapy or Cabo. Pts underwent a baseline biopsy and received Nivo 3 mg/kg and Ipi 1 mg/kg intravenously Q3 weeks (W) for 4 cycles followed by Nivo 480 mg IV Q4W. Cabo was given continuously at a dose of 20 mg/d; reductions to 20 mg every other day were allowed; after completion of Ipi, the Cabo dose could be increased to 40 mg/d. The primary endpoint was ORR by RECIST 1.1. Safety was a secondary endpoint. A one-stage design with 20 subjects (for 7 or more responses) would provide 75% power to distinguish an ORR of 40% versus 20% at one-sided alpha of 0.1. **Results:** 20 pts were enrolled and received at least 1 study drug at 7 sites from Feb. 2023 to Apr. 2024. Following histologic subtypes were included: papillary (n = 11), chromophobe (n = 1), translocation (n = 3), unclassified RCC (n = 2) and other (n = 3). 4 (20%) pts received prior systemic therapy. 10 (50%) pts received all 4 doses of Nivo and Ipi; 13 (65%) pts received maintenance nivolumab. Cabo was increased to 40 mg in 11/13 of these patients. Median follow-up was 9.4 (range 4.6-17.7) months. ORR was 25% (5/20, two-sided 80% CI, 13-41%, Table 1). 6- and 12-month progression free survival rates were 65% and 42% respectively. 11 (55%) pts developed grade 3 or 4 TrAEs (6 were due to elevation in liver function tests) and 1 (5%) had grade 5 TrAE (intraoperative hemorrhage) in setting of disease progression. 5 (25%) required high dose steroids (≥40 mg prednisone or equivalent) of which only 3 (15%) received for hepatitis. All therapy was discontinued due to toxicity in 1 (5%) pt. **Conclusions:** Although the study did not reach the target of 7 responses to uphold the alternative hypothesis, reduction of the starting dose of Cabo to 20 mg/d in combination with Nivo/Ipi results in numerically lower ≥ grade 3 TrAEs than starting at 40 mg/d (60% vs 77%) and clinical activity in a subset of patients. Clinical trial information: NCT04413123. Research Sponsor: Exelixis; BMS.

	Total (N=20)	Histology					Prior Systemic Therapy	
	N(%)	Papillary	Chromophobe	Translocation	Unclassified RCC	Other	No	Yes
PR	5 (25)	2	1	0	2	0	4	1
SD	8 (40)	5	0	2	0	1	7	1
PD	7 (35)	4	0	1	0	2	5	2

PR=partial response, SD=stable disease, PD=progressive disease.

Efficacy of second line (2L) treatment with tivozanib (Tivo) as monotherapy or with nivolumab (Nivo) in patients (pts) with metastatic renal cell carcinoma (mRCC) previously treated with an immune checkpoint inhibitor (ICI) combination of ipilimumab (Ipi)/Nivo or vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI)/ICI in the phase 3 TiNivo-2 study.

Alex Chehrazi-Raffle, Robert J. Motzer, Katy Beckermann, Philippe Barthelemy, Roberto Iacovelli, Sheik Emambux, Javier Molina Cerrillomd, Benjamin Garmezy, Pedro C. Barata, Rana R. McKay, Hans J. Hammers, Daniel Yick Chin Heng, Bo Jin, Claudia Lebedinsky, Edgar E. Braendle, Bradley Alexander McGregor, Laurence Albiges, Toni K. Choueiri; City of Hope Comprehensive Cancer Center, Duarte, CA; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Vanderbilt University, Nashville, TN; Institut de Cancérologie Strasbourg Europe, Strasbourg, France; Comprehensive Cancer Center, Oncology Unit, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy; Centre Hospitalier Universitaire de Poitiers, Poitiers, France; Hospital Universitario Ramón y Cajal, Madrid, Spain; Sarah Cannon Research Institute, Nashville, TN; University Hospitals Seidman Cancer Center, Cleveland, OH; University of California San Diego, San Diego, CA; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; AVEO Oncology, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Gustave Roussy, Paris Saclay University, Paris, France; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: In TiNivo-2, the addition of Nivo to Tivo did not prolong progression-free survival (PFS) relative to Tivo alone (Choueiri, Lancet 2024). To assess study outcomes in the context of contemporary treatment sequencing, a subset of pts treated in the 2L who failed 1L Ipi/Nivo or VEGFR-TKI/ICI therapy was evaluated. **Methods:** Pts were randomized 1:1 to receive Tivo once daily for 21/28 days at either 1.34mg alone or at 0.89 mg with Nivo at 480 mg by IV on day 1 of each 28-day cycle. We characterized PFS, objective response rate (ORR), and best percentage change from baseline in tumor size in two cohorts consisting of pts who did not previously receive adjuvant therapy and who progressed in 1L on Ipi/Nivo, or VEGFR-TKI/ICI therapy. **Results:** Among the 153 eligible 2L pts, 70 (46%) previously received Ipi/Nivo and 83 (54%) previously received a VEGFR-TKI/ICI regimen (TKI/ICI): axitinib/pembrolizumab (54.2%), cabozantinib/nivolumab (25.3%), axitinib/avelumab (12.0%), and lenvatinib/pembrolizumab (8.4%). Overall, the median follow-up was 11.6 months. More pts with lung metastasis and age <65 years were in the Tivo arm than in the Tivo+Nivo arm in both cohorts. In the Ipi/Nivo cohort, median PFS was 9.2 months (95% CI, 4.5-NR) with Tivo and 9.3 months (95% CI, 7.3-15.3) with Tivo+Nivo. ORR was 32.4% (95% CI, 18.0%-49.8%) with Tivo and 24.2% (95% CI, 11.1%-42.6%) with Tivo+Nivo. In the TKI/ICI cohort, median PFS was 7.4 months (95% CI, 3.7-9.3) with Tivo and 3.9 months (95% CI, 2.1-5.7) with Tivo+Nivo. ORR was 22.0% (95% CI, 10.6%-37.6%) with Tivo and 9.5% (95% CI, 2.7%-22.6%) with Tivo+Nivo. Target tumor size reduction from baseline was observed in both arms (Table). More pts had target tumor reductions (≥30% or ≥50%) in the Tivo arm than in the Tivo+Nivo arm in both cohorts. Of 7 pts with target tumor reduction of ≥50% from Tivo, 6 (85.7%) and 1 (14.3%) were previously treated with axitinib and cabozantinib, respectively. **Conclusions:** In this TiNivo-2 subgroup analysis, Tivo monotherapy at 1.34 mg daily showed activity in pts who previously received a contemporary 1L mRCC regimen. At this dose of Tivo, substantial tumor size reduction was observed, both after Ipi/Nivo and VEGFR-TKI/ICI regimens. There appeared to be no benefit with the addition of Nivo to Tivo in this context, akin to the results of the parent trial. Clinical trial information: NCT04987203. Research Sponsor: AVEO Oncology.

Best percentage change in target tumor size.

		Best % Change from Baseline	
	Prior Treatment	≥30% Reduction	≥50% Reduction
Tivo	TKI/ICI	30.5%	19.4%
	Ipi/Nivo	44.4%	27.8%
Tivo+ Nivo	TKI/ICI	17.5%	2.5%
	Ipi/Nivo	33.3%	12.1%

Neoadjuvant lenvatinib plus pembrolizumab for resectable clear-cell renal cell carcinoma (PELUR): A prospective phase 2 study.

Shimiao Zhu Sr., Changyi Quan Sr., Haotian Wei Sr.; Tianjin Institute of Urology, the Second Hospital of Tianjin Medical University, Tianjin, China; The Second Hospital of Tianjin Meidical University, Tianjin, China; The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Lenvatinib plus pembrolizumab prolongs overall survival (OS) and progression-free survival (PFS) in advanced clear-cell renal cell carcinoma (ccRCC), with significantly improved objective response rate (ORR) and survival time compared with other competitors. However, more than 80% ≥Grade 3 adverse events (AEs) were emerged during treatment. The efficacy and safety of neoadjuvant low-dose lenvatinib plus pembrolizumab (ldLP) in ccRCC at high-risk of progression has not been assessed. **Methods:** This was an open-label phase 2 clinical trial including patients with resectable high-risk ccRCC who received neoadjuvant ldLP every 21 days for 3 cycles. Tumor responses and safety were both primary end points. The secondary end points were PFS, patient-reported quality-of-life and immune biomarkers. RNA and DNA were isolated from pretreatment tumor tissue was subjected to RNA and next-generation sequencings. Single-cell RNA sequencing (scRNA-seq) was performed in both pretreatment and posttreatment specimens from 6 patients. **Results:** A total of 33 patients were enrolled, 23 received neoadjuvant therapy followed by nephrectomy were included in the intention-to-treat (ITT) analysis. All patients received neoadjuvant therapy follow the dose of protocol. There was only one grade 3 AE (hypertension) emerged during neoadjuvant therapy. The most common AEs of neoadjuvant treatment were hypertension, fatigue, rash and pruritus (n = 5, 21.7%). During adjuvant stage, three grade 3 AEs were reported, including one case of rash, ALT/AST increase and acute kidney injury. The most common AEs during adjuvant were rash, fatigue and pruritus (n = 6, 26.1%). The EORTC QLQ-C30 questionnaires showed significant improvements in all emotional function and symptom of appetite loss. Total score of FKSI-DRS was also significantly improved. Tumor and thrombus regression occurred in all patients after neoadjuvant therapy, with 11/23 (47.8%) of them got partial response. After a median follow-up of 22 months (15-35 months), five patients experienced disease progression and 2 patients had ccRCC-related died. We characterized ~11500 single cells from 6 patients (12 samples), which were categorized into partial response (PR; n = 3) and stable disease (SD; n = 3). Our analysis revealed that the $ARPP21^+$/$IGLL1^+$ B cell subcluster (AI^+ B cells) demonstrated the most substantial cellular perturbation within SD group. Furthermore, we observed AI^+ B cells experienced a significant reduction in PR group following treatment. The AI^+ B cells were predicted to interact with DCs to contribute to a poor therapy response. **Conclusions:** Our data preliminarily demonstrated safety and efficacy of neoadjuvant ldLP in ccRCC at high-risk of progression. Results also highlight the importance of AI^+ B cells in effective responses to ldLP and suggests potential strategies to overcome immunotherapy resistance. Clinical trial information: NCT05485896. Research Sponsor: National Natural Science Foundation of China (82172759); Tianjin Education Commission Research Program Project (2024ZD026 & 2024KJ193); Tianjin Municipal Health Science and Technology Project (TJWJ2024ZD002).

Clear and non-clear cell renal cell carcinomas and the ability to engage in oxidative phosphorylation.

Ziad Bakouny, Sonia Boscenco, Ruobing Cui, Keunwoo Ryu, Ritesh R. Kotecha, Marie Carlo, Martin H. Voss, A. Ari Hakimi, Robert J. Motzer, Payam A Gammage, Eduard Reznik, Craig B. Thompson; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer, New York, NY; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; School of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom

Background: The impairment of oxidative phosphorylation (OxPhos) and upregulation of aerobic glycolysis, mediated by the loss of *VHL*, are key features of clear cell renal cell carcinoma (ccRCC). In contrast, non-clear cell renal cell carcinoma (RCC) denotes a heterogeneous group of tumors with few known nuclear oncogenic drivers. Recent studies have shown that mitochondrially-encoded electron transport chain (ETC) genes, responsible for OxPhos, can be mutated in a range of cancers. **Methods:** Mitochondrial mutations were called using a previously published custom pipeline for variant calling (PMID: 33833465). On-target (whole genome sequencing) and off-target (whole exome and gene panel-based sequencing) reads were used. Only samples with sufficient coverage ($>$ = 5 reads across $>$ 90% of the mitochondrial genome) were included. This was performed (N with sufficient coverage) in TCGA (N = 3,265; N = 324 RCC), the institutional MSK-IMPACT cohort (N = 22,252; N = 568 RCC), and CCLE/Depmap (N = 377; N = 11 RCC). Mutual exclusivity between each established RCC nuclear driver gene (N = 16, PMID: 29617669) and the heteroplasmy of ETC truncating variants was evaluated using pairwise t-tests comparing heteroplasmy between the mutated and wild-type RCC samples for each nuclear driver gene. CERES scores from genome-wide CRISPR screens in Depmap were used to compare gene dependency between cell lines. Benjamini-Hochberg correction was used to control type I error. **Results:** Across all cancer types in TCGA, RCC tumors were among the most enriched in ETC truncating mutations. These mutations most frequently affected components of mitochondrial complex I and were enriched to high levels of heteroplasmy. *VHL*-driven ccRCC was relatively depleted in these mutations compared to other subtypes (ccRCC: 8.6%, chRCC: 20.0%, pRCC: 34.0%). Further, the heteroplasmy of truncating mutations was significantly increased in chRCC and pRCC compared to ccRCC ($p < 0.05$). Among all established RCC nuclear driver genes, *VHL* was found to be mutually exclusive with high heteroplasmy ETC truncating mutations ($q < 0.05$). These results were independently replicated in the MSK-IMPACT cohort. Using data from CCLE/Depmap, we find that while cell lines with high heteroplasmy ($>$ 50%; N = 13) truncating mitochondrially-encoded ETC mutations have differential dependencies compared to other cell lines, ETC mutations were not synthetically lethal with *VHL* mutations. Further, knockout of nuclear ETC components of complex I in Depmap was associated with little to no effect on cell survival. **Conclusions:** We established that mutations in *VHL* and in mitochondrially-encoded ETC genes are mutually exclusive in RCC and that this mutual exclusivity is not accounted for by synthetic lethality. These results suggest that mitochondrial mutations may be phenocopying the effect of *VHL* on OxPhos. Research Sponsor: National Cancer Institute; T32CA009512-35; National Cancer Institute; P30-CA008748.

4543 Poster Session

HIF family transcription factor expression in a cohort of 4362 patients with renal cell carcinoma (RCC).

Yu-Wei Chen, Shayan S. Nazari, Andrew Elliott, Ninad Kulkarni, Norm Smith, Rashad Nawfal, Pedro C. Barata, Brent S. Rose, Aditya Bagrodia, Neeraj Agarwal, Sumanta Kumar Pal, Toni K. Choueiri, Rana R. McKay; Moores Cancer Center at UC San Diego Health, San Diego, CA; Caris Life Sciences, Phoenix, AZ; Caris Life Sciences, Irving, TX; Dana-Farber Cancer Institute, Boston, MA; University Hospitals Seidman Cancer Center, Cleveland, OH; University of California, San Diego, San Diego, CA; University of California San Diego Health, La Jolla, CA; Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT; Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Moores Cancer Center, University of California San Diego, La Jolla, CA

Background: The HIF pathway drives RCC pathogenesis operating through transcription factors (TFs) that function as heterodimers of the oxygen-sensitive α (HIF1α or HIF2α) and constitutively expressed β subunits (HIF1β or HIF2β). Loss of VHL leads to HIFα stabilization, nuclear translocation, and formation of transcriptional complexes with β subunits. We aimed to characterize the molecular and clinical features associated of HIF TF mRNA expression in RCC. **Methods:** NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed on RCC specimens (n = 4362) at Caris Life Sciences. HIF-High/Low expression was defined as $> 75^{th}$ / $< 25^{th}$ quartile RNA transcripts per million (TPM). Overall survival (OS) was defined as the time of diagnosis to death/last follow-up. Time on treatment (TOT) was defined as the time from treatment start to discontinuation. **Results:** The majority of patients were male (71%), of white race (61%), with median age of 64 years. HIF2α was lower in tumors from Black vs White patients (102.3 vs 157.5 TPM, $p < 0.0001$) and higher in tumors from Hispanic vs non-Hispanic White patients (146.1 vs 195.4 TPM, $p < 0.01$). Compared to kidney primary (n = 1,784, 43.9%, 172.1 TPM), HIF2α expression was lower in lymph nodes (n = 319, 7.9%, 97.6 TPM, $p < 0.01$) but similar to distant metastatic sites (n = 1,959, 48.2%, 168.3 TPM). Compared to clear cell RCC (n = 1198, 29.5%, 224.3 TPM), HIF2α expression was lower in papillary (n = 238, 5.9%, 57.5 TPM), chromophobe (n = 83, 2.0%, 91.7 TPM), and medullary RCC (n = 15, 0.36%, 46.5 TPM) ($p < 0.01$ each). Sarcomatoid RCC (n = 119, 2.9%) had lower HIF2α (111.9 vs. 155.0 TPM, $p < 0.05$), lower HIF2β (5.6 vs 8.5 TPM, $p < 0.01$), and higher HIF1α (276.3 vs 197.4 TPM, $p < 0.01$) compared to non-sarcomatoid RCC (n = 3947, 97.2%). Compared to *VHL* wild-type (n = 1415, 34.9%), *VHL*-mutated tumors (n = 1884, 46.4%) had higher HIF2α (206.6 vs 97.7 TPM), lower HIF1α (184.9 vs 233.9 TPM), lower HIF2β (7.2 vs 10.2 TPM) ($p < 0.01$ each). Tumors with high HIF2α were enriched for *VHL*, *PBRM1*, *MTOR*, and *PTEN* alterations and had fewer *TP53*, *BAP1*, *MET*, *SMARCB1*, and *NF2* alterations. HIF1α-high tumors had fewer *VHL*, *TSC1*, and *BAP1 alterations*. HIF1β -high tumors had decreased *TP53* and *RB1* and increased *CHEK2* and *PALB2* alterations. High HIF2α and HIF2β was associated with improved OS (92.6 vs 68.1 months, $p < 0.001$ and 87.4 vs 69.8 months, $p < 0.004$, respectively), while HIF1α and HIF1β did not correlate with OS. Patients with high HIF2α had prolonged cabozantinib TOT (8.1 vs 3.9 months, $p < 0.001$). **Conclusions:** This comprehensive analysis revealed distinct HIF TF expression patterns across RCC subgroups. Notably, elevated HIF2α expression was observed in clear cell RCC, VHL-mutated tumors, and was linked to improved OS and prolonged TOT with cabozantinib, suggesting a potential prognostic role for HIF2α in RCC, warranting further clinical investigation. Research Sponsor: None.

Baseline radiological tumor burden to sub-stratify IMDC risk groups in metastatic renal cell carcinoma treated with first-line therapy: A post hoc analysis from a randomized phase III trial.

Rashad Nawfal, Razane El Hajj Chehade, Karl Semaan, Marc Eid, Liliana Ascione, Eddy Saad, Wassim Daoud Khatoun, Mustafa Jamal Saleh, Jad El Masri, Wenxin Xu, Emre Yekeduz, Maxine Sun, David A. Braun, Saurabh Gupta, Daniel Yick Chin Heng, Katherine Krajewski, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Center of Molecular and Cellular Oncology, Yale University, New Haven, CT; Bristol Myers Squibb, Princeton, NJ; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; Department of Radiology, Brigham and Women's Hospital, Boston, MA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Baseline radiological tumor burden (BRTB) is a measurement derived from routine CT scans and reflects baseline tumor burden. Herein we assess the utility of BRTB to help with risk assessment within IMDC risk subgroups from a randomized prospective phase III study. **Methods:** We reviewed data of 701 patients with metastatic renal cell carcinoma (mRCC) from the CheckMate 9ER trial (Choueiri, NEJM 2021). Patients with BRTB measurement per investigator using RECIST v1.1 at baseline were included. Outcomes of interest included overall survival (OS), and progression-free survival (PFS). To evaluate the impact of BRTB on OS and PFS, we used univariate and multivariable Cox regression models for each IMDC subgroup accounting for age, sex, race, stage at diagnosis, sarcomatoid features and regimen type (IO+VEGFi, VEGFi). **Results:** Favorable, intermediate and poor risk IMDC subgroups included 157/701, 392/701 and 132/701 patients, respectively. This cohort included 63, 187 and 94 OS events and 112, 290 and 103 PFS events in favorable, intermediate and poor risk groups, respectively. For the favorable risk group, BRTB was not associated with OS or PFS on multivariable analysis ($HR_{adjusted}$= 1.00, 95%CI: 0.99-1.01, p = 0.68 and $HR_{adjusted}$= 1.00, 95%CI: 0.99 – 1.00, p = 0.99, respectively). Similarly for the poor risk group, BRTB was not associated with OS or PFS on multivariable analysis ($HR_{adjusted}$= 1.03, 95%CI: 0.99-1.06, p = 0.06 and $HR_{adjusted}$= 1.02, 95%CI: 0.98 – 1.04, p = 0.54, respectively). However, in the intermediate risk group, higher BRTB was associated with worse OS (HR: 1.05 for each 1 cm increase in BRTB, 95%CI: 1.04-1.07, $p < 0.0001$) and PFS (HR: 1.03, 95%CI: 1.01-1.05, $p < 0.001$). On multivariable analysis, BRTB remained associated with both OS and PFS ($HR_{adjusted}$= 1.05, 95%CI: 1.04-1.07, $p < 0.0001$ and $HR_{adjusted}$= 1.03, 95%CI: 1.02 – 1.05, $p < 0.0001$, respectively). Further, we stratified IMDC intermediate risk group outcomes according to BRTB median value of 6.33cm (Table). **Conclusions:** While BRTB does not appear to predict outcomes in favorable and poor-risk subgroups in this study, BRTB is a useful metric for sub-stratification of the intermediate-risk IMDC subgroup. External validation is imperative to validate these findings and explore BRTB integration into clinical decision-making in mRCC. Research Sponsor: None.

Stratification of the intermediate IMDC risk group according to baseline radiological tumor burden median (6.33cm).

	Intermediate low BRTB (n=196)	Intermediate high BRTB (n=196)	Log rank p value
Median OS, months (95% CI)	NR (49.5 – NR)	30.9 (24.4 – 40)	$p < 0.0001$
Median PFS, months (95% CI)	15.84 (11.83 – 18.3)	8.41 (6.97 – 11.1)	$p < 0.001$

Efficacy of subsequent treatment after combination therapy in non-clear cell renal cell carcinoma (nccRCC).

Paulo Siqueira do Amaral, Aniko Szabo, Clara Hwang, Pooja Ghatalia, Abhishek Tripathi, Hannah Dzimitrowicz McManus, Hamid Emamekhoo, Jennifer King, Benjamin L. Maughan, Yousef Zakharia, Pedro C. Barata, Arpita Desai, Melissa A. Reimers, Yasser Ged, Elisabeth I. Heath, Mehmet Asim Bilen, James Brugarolas, Brian I. Rini, Rana R. McKay, Deepak Kilari; Vandebilt University Medical Center, Nashville, TN; Division of Biostatistics, Froedtert and The Medical College of Wisconsin, Milwaukee, WI; Division of Hematology/Oncology, Department of Internal Medicine, Henry Ford Cancer, Detroit, MI; Fox Chase Cancer Center, Philadelphia, PA; City of Hope Comprehensive Cancer Center, Duarte, CA; Duke Cancer Center, Durham, NC; University of Wisconsin-Madison, Madison, WI; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Mayo Clinic, Phoenix, AZ; University Hospitals Seidman Cancer Center, Cleveland, OH; University of California, San Francisco, San Francisco, CA; Department of Medicine, Division of Oncology, Washington University School of Medicine, St. Louis, MO; Johns Hopkins University School of Medicine, Baltimore, MD; Mayo Clinic, Rochester, MN; Winship Cancer Institute of Emory University, Atlanta, GA; UT Southwestern Medical Center, Dallas, TX; Vanderbilt University Medical Center, Nashville, TN; University of California, San Diego, CA; Department of Medicine, Division of Hematology and Oncology, The Medical College of Wisconsin, Milwaukee, WI

Background: The treatment landscape of front-line nccRCC has evolved with recent trials demonstrating the efficacy of combination systemic therapy. However, the efficacy of treatment after combination therapy is unknown. This study evaluates the efficacy of VEGF-based regimens in nccRCC patients (pts) previously treated with combination regimens. **Methods:** ORACLE is a real-world, multi-center, retrospective database that includes nccRCC patients that received combination systemic therapies (IO+IO, IO+VEGF and VEGF+ mTOR) in any line. Subsequent treatments were categorized as VEGF only regimens (cabozantinib vs other VEGF), IO+ VEGF and VEGF+ mTOR. The primary endpoint was objective response rate (ORR) assessed by investigator review using RECIST 1.1. Secondary endpoints included disease control rate (DCR), defined as the proportion of patients achieving complete or partial responses or stable disease, time to treatment progression (TTP), calculated from the date of VEGF-based initiation to progression or last follow-up using the Kaplan-Meier method. Differences between groups were estimated with the log-rank test, and categorical outcomes were compared with the chi-square test. **Results:** 105 pts who received VEGF – based regimens after combination therapy were included in the analysis. Baseline characteristics: median age: 59years, 71% male, 58% white, 25% black, 87% ECOG 0-2. IMDC-risk categories included:21% favorable, 59% intermediate and 20% poor risk. Histology included papillary (40%), unclassified (32%), chromophobe (16%) and other rare subtypes (12%). Prior combination therapies included IO+IO: 62%, IO+ VEGF: 34% and VEGF+ mTORi:4%. 70% pts received combination therapy in the first line setting while the remainder received combination therapy in a second or later line. Outcomes with subsequent treatments are described in Table1. IMDC risk score correlated with TTP. **Conclusions:** Modest antitumor activity was observed with VEGF- based approaches in combination therapy refractory nccRCC. Optimal management of nccRCC remains an unmet need. Research Sponsor: None.

Outcomes of nccRCC patients by treatment and histologic type.

Outcomes per Treatment	n	ORR (%)	DCR (%)	mTTP (mo.)
Cabozantinib	56	18	47	3.6
VEGF/mTOR	19	16	42	9.3
IO+VEGF	17	29	47	5.6
Other VEGF	13	15	46	5.5
Outcomes per Histology				
Papillary	42	19	43	6.5
Unclassified	33	21	42	6.1
Chromophobe	17	29	59	8.9
Other *	13	0	46	NR

Integrative clinical, genomic, and transcriptomic characterization of circulating KIM-1 in metastatic RCC.

Marc Machaalani, Renee Maria Saliby, Eddy Saad, Clara Steiner, Caiwei Zhong, Emre Yekeduz, Xiaowen Liu, Marc Eid, Razane El Hajj Chehade, Liliana Ascione, Jad El Masri, Mustafa Jamal Saleh, Ti Cai, Maxine Sun, Gwo-Shu Mary Lee, Wanling Xie, Sabina Signoretti, David F. McDermott, Toni K. Choueiri, Wenxin Xu; Dana-Farber Cancer Institute, Boston, MA; Yale Cancer Center, New Haven, CT; Beth Israel Deaconess Medical Center, Boston, MA; EMD Serono Research and Development Institute, Billerica, MA; Brigham and Women's Hospital, Boston, MA

Background: Kidney injury molecule-1 (KIM-1) is a transmembrane protein that is overexpressed in renal cell carcinoma (RCC) and correlated with clinical outcomes in localized and metastatic disease. Nevertheless, association between circulating KIM-1 protein levels and the underlying tumor biology represented by genomic and transcriptomic correlates is not well understood. **Methods:** KIM-1 was measured in plasma at baseline (C1D1) and at C3D1 using an MSD electrochemiluminescence-based assay. Differential gene expression (DGE) and gene set enrichment analysis (GSEA) were performed using DESeq2, with KIM-1 treated as a continuous variable. Associations between circulating KIM-1 levels and clinical, genomic, and transcriptomic tissue data from the JAVELIN Renal 101 trial were evaluated using the Wilcoxon rank-sum test (for categorical groups) and Cox regression (for time-to-event outcomes). **Results:** Plasma for analysis was available from 612 patients (69% of the ITT population), including 323 treated with avelumab plus axitinib and 289 with sunitinib. Elevated baseline KIM-1 levels were correlated with higher tumor burden as assessed by the sum of tumor diameters (Spearman's $\rho = 0.55$, $p < 0.0001$), decreased with tumor shrinkage ($p < 0.0001$), and were associated with poorer PFS (HR 1.32 per unit increase in log KIM-1, 95% confidence interval (CI) 1.16–1.49, $p < 0.0001$) and OS (HR 1.96 per unit increase in log KIM-1, 95% CI 1.61–2.37, $p < 0.0001$). Higher KIM-1 levels were found in IMDC poor–risk versus intermediate–risk ($p < 0.0001$) and in intermediate–risk versus favorable–risk groups ($p < 0.001$). Loss-of-function (LOF) *BAP1* mutations, associated with more aggressive disease, were associated with higher KIM-1 RNA expression ($p < 0.0001$) and protein expression ($p = 0.038$) and remained significant after adjustment for tumor burden as assessed by linear regression residuals. Transcriptomic analysis showed that RNA expression levels of *HAVCR1*, the gene coding KIM-1, were associated with circulating KIM-1 protein (Spearman's $\rho = 0.31$, $p < 0.0001$), and that higher KIM-1 levels were associated with interferon gamma response whereas lower KIM-1 levels were associated with a hypoxia transcriptional program. Higher circulating KIM-1 was also associated with enrichment for proliferative versus angiogenic gene expression signatures ($p = 0.013$). The findings were independent of therapy arms. **Conclusions:** We present the first integrative clinical, transcriptomic, and genomic evaluation of circulating KIM-1. High KIM-1 is a biomarker of poor prognosis in RCC and correlates with specific LOF mutations and transcriptions programs. Prospective studies are needed for the clinical implementation of KIM-1 as a biomarker in RCC. Research Sponsor: U.S. National Institutes of Health; CA258442; Dana-Farber/Harvard Cancer Center Kidney SPORE; 2P50CA101942-16.

KEAP1 mutated renal cell carcinoma (RCC): Characterization of an emerging molecularly defined RCC subtype.

Marie Carlo, Ying-Bei Chen, Andrea Knezevic, Grace Zong, Ziad Bakouny, Yelena Kemel, Alicia Latham, Ying L. Liu, Neil J. Shah, Darren R. Feldman, Ritesh R. Kotecha, Miika Mehine, Diana Mandelker, Zsofia Kinga Stadler, Eduard Reznik, Michael F. Berger, Martin H. Voss, Robert J. Motzer, Kenneth Offit, A. Ari Hakimi; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center and Weill Medical College, New York, NY

Background: KEAP1 is a tumor suppressor and negative regulator of the NRF2 pathway, and inactivating *KEAP1* mutations (mts) have been reported in patients (pts) with RCC with similar morphology to fumarate hydratase (FH)-deficient RCC (FH-RCC). In FH-RCCs, the NRF2 pathway is activated through fumarate-led inactivation of KEAP1, and we hypothesized that *KEAP1* mts are drivers in RCC, similar to FH mts in FH-RCC. We sought to characterize RCC with *KEAP1* mts as a separate RCC subtype and compare to FH-RCC and clear cell (cc)RCC. **Methods:** Among consecutive pts with RCC consented to tumor-normal DNA sequencing via MSK-IMPACT (NCT01775072), we identified patients with germline or somatic mutations in *KEAP1* or *FH* and no other known driver mts (ie *VHL*, *MET*, *TFE3* alterations), and categorized these as "KEAP1-RCC" or "FH-RCC." Clinicopathologic characteristics and outcomes were analyzed and compared to pts with FH-RCC and a previously annotated subset ccRCC (n=162). Immunohistochemical (IHC) staining for NQO1, marker of NRF2 activation, was performed. Time on systemic treatment and overall survival (OS) from time of sequencing were assessed. **Results:** Among 928 pts with RCC, 13 (1.4%) and 26 (2.8%) had RCCs with *KEAP1* and *FH* mts, respectively. *KEAP1* and *FH* mts were mutually exclusive. Median age was younger in FH-RCC (47 vs 63) (Table). When compared to ccRCC, OS was significantly worse for FH-RCC (HR 2.4, 95% CI 1.4-4.1; p=0.02) but not for KEAP1-RCC (HR 1.07, 95% CI 0.29-3.0; p=0.89). All KEAP1-RCC and FH-RCC were histologically classified as non-cc except one KEAP1-RCC that had 3p loss and no VHL mt. All available KEAP1 and FH-RCC were NQO1+ on IHC; control ccRCC were all negative. In the KEAP1-RCC cohort, we identified a female with an unclassified RCC and a germline *KEAP1* truncating variant; RCC tumor had a second *KEAP1* somatic mutation and was NQO1+ on IHC. The germline variant cosegregated to a sister with lung cancer (IHC NQO1+) and anal cancer. **Conclusions:** RCC with KEAP1 mts and no other genomic drivers are primarily non-cc with papillary features, have functional evidence of NRF2 activation, and although high-grade may have better outcomes than FH-RCC. KEAP1-RCC appears to be an emerging molecularly defined RCC subtype with clinical behavior similar to FH-RCC, likely as a result of converging on NRF2 pathway activation. Research Sponsor: National Cancer Institute; Mazumdar-Shaw Translational Research Initiative in Kidney Cancer; Robert and Kate Niehaus Center for Inherited Cancer Genomics.

Clinical characteristics.

	KEAP1-RCC (n=13)	FH-RCC (n=26)	ccRCC (n=162)
Age (range)	63 (26-71)	47 (20-74)	56 (24-78)
Male	8 (62%)	17 (65%)	125 (77%)
Tumor size (cm), median (IQR)	5.6 (5.1, 11.0)	8.0 (5.0, 14.0)	8.2 (6.0, 10.5)
Histology			
FH-deficient	0	13 (50%)	0
Papillary features	8 (62%)	4 (15%)	0
Unclassified	1 (8%)	8 (31%)	0
ccRCC	1 (8%)	0	162 (100%)
Other/Unknown	3 (23%)	1 (4%)	0
Tumor grade, high	13 (100%)	26 (100%)	134 (83%)
Metastatic	9 (69%)	25 (96%)	150 (93%)

Second-line outcomes in metastatic renal cell carcinoma: The role of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic factors after first-line immunotherapy.

David Maj, Martin Zarba, Connor Wells, Marc Eid, Razane El Hajj Chehade, Zeynep Irem Ozay, Joe Elie Dib, Ulka N. Vaishampayan, Sumanta Kumar Pal, Thomas Powles, Arnoud J. Templeton, Naveen S. Basappa, Shirley Wong, Andrew Weickhardt, Aly-Khan A. Lalani, Ravindran Kanesvaran, Guillermo de Velasco, Martin Angel, Toni K. Choueiri, Daniel Yick Chin Heng; Arthur J.E. Child Comprehensive Cancer Centre, Calgary, AB, Canada; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; University of Michigan, Ann Arbor, MI; Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA; Department of Medical Oncology, St. Claraspital Basel and Faculty of Medicine, University of Basel, Basel, Switzerland; Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; Western Health, Melbourne, VIC, Australia; Olivia Newton John Cancer Research Institute, Heidelberg, VIC, Australia; Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; National Cancer Centre Singapore, Singapore, Singapore; Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; Instituto Alexander Fleming, Buenos Aires, Argentina; Arthur JE Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: IMDC prognostic factors are well established in metastatic renal cell carcinoma (mRCC) with both VEGFR inhibitor and immunotherapy-based first-line therapies. However, the role of these prognostic factors for the second-line setting is less established in the contemporary era. **Methods:** We performed a retrospective analysis of patients with mRCC who received first-line therapy (1L) with dual immunotherapy (IPI-NIVO) or combination immunotherapy-VEGFR (IOVE) based regimens and then received second-line therapy (2L). 2L IMDC risk factors were assessed at the time of 2L therapy initiation and were composed of Karnofsky Performance Status < 80%, time from diagnosis to 2L therapy start < 1 year, hemoglobin < lower limit of normal, neutrophils > upper limit of normal (ULN), platelets > ULN, corrected calcium > ULN. 2L IMDC risk groups were favorable (0 risk factors), intermediate (1-2 risk factors), or poor risk (3+ risk factors). Baseline characteristics, objective response rates (ORR), treatment duration (TD), and overall survival (OS) were collected and compared by log-rank test. **Results:** A total of 781 patients were identified of whom 66% received IPI-NIVO and 34% received IOVE in the 1L setting. 2L IMDC risk groups and changes from 1L IMDC risk are presented in Table. Amongst all patients who received 2L therapies, 10.6% had favorable risk, 57.8% had intermediate risk, and 31.6% had poor risk disease. Nephrectomy status varied significantly across groups with 99% of favourable risk, 65% of intermediate risk, and 42% of poor risk patients having undergone nephrectomy ($p<0.0001$). Overall, 66.3% of patients retained their 1L risk group, while 12.6% were in a more favorable risk group and 21.1% a less favorable risk group. Type of 1L therapy (IPI-NIVO vs IOVE) did not predict change in 2L IMDC risk group ($p=0.931$). 2L therapies were heterogeneous with 38.9% receiving cabozantinib, 22.3% sunitinib, 8.7% pazopanib, 12.7% an IO-based regimen (IO monotherapy, IOIO, IOVE), and 17.4% other therapies. 2L ORR, TD, and OS varied significantly by 2L IMDC risk group (Table). **Conclusions:** In a real-world setting amongst patients receiving 1L IO-based regimens, IMDC risk factors remain prognostic in the 2L setting. These new benchmarks may be used for patient counselling and clinical trial design in 2L. Research Sponsor: None.

Baseline characteristics and outcomes by 2L IMDC risk group.

	2L Favorable N = 83	2L Intermediate N = 451	2L Poor N = 240	P-value
1L IPI-NIVO/IOVE	35/48	306/145	197/50	
1L Favorable, N (%)	**50 (50)**	45 (45)	5 (5)	
1L Intermediate, N (%)	21 (5.2)	**284 (70.6)**	97 (24.1)	
1L Poor, N (%)	2 (1)	65 (33.3)	**128 (65.6)**	
2L ORR, N (%)	26 (38.2)	114 (32.0)	40 (22.9)	<0.0001
2L TD, Mo (95%CI)	9.8 (8.1-18.5)	9.1 (8.1-10.0)	4.2 (3.2-5.4)	<0.0001
2L OS, Mo (95%CI)	41.0 (35.7-NR)	25.9 (20.5-32.1)	9.4 (7.1-10.8)	<0.0001

Clinical characteristics and determinants of primary refractory metastatic renal cell carcinoma (mRCC): An International Metastatic Database Consortium (IMDC) study.

Karl Semaan, Marc Eid, Wanling Xie, Razane El Hajj Chehade, Liliana Ascione, David Maj, Martin Zarba, Connor Wells, Ulka N. Vaishampayan, Martin Angel, Jae Lyun Lee, Kosuke Takemura, Christian K. Kollmannsberger, Georg A. Bjarnason, Jose Manuel Ruiz-Morales, Daniel Yick Chin Heng, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; University of Michigan, Ann Arbor, MI; Alexander Fleming Institute, Buenos Aires, Argentina; Asan Medical Center, Seoul, South Korea; British Columbia Cancer Agency, Vancouver, BC, Canada; Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; Hospital Medica Sur, Toriello Guerra, DF, Mexico; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Immune checkpoint inhibitor (ICI)-based regimens, including ICI + ICI and ICI+VEGF-targeted therapy (VEGF-TT), represent the current standard of care for first line (1L) in mRCC. A subset of patients (pts) experiences primary refractory disease, defined as progressive disease (PD) as best response. The aim of this study is to investigate the clinical characteristics and determinants of pts with primary refractory mRCC. **Methods:** Pts with mRCC treated with 1L ICI-based regimens from the IMDC were included. Pts were categorized as primary refractory (PD as best response evaluated per RECIST 1.1 criteria) and non-primary refractory (stable disease or partial/complete response as best response). Baseline characteristics were compared using a Chi-Square test. Independent factors associated with primary refractory mRCC were identified using a logistic regression. **Results:** In total, 2001 pts were included, of which 1301 (65%) were treated with dual ICI, and 701 (35%) with ICI+VEGF-TT. Of 2001 pts, 494 (24%) experienced PD at first restaging. Primary refractory and non-primary refractory groups did not differ by age or gender. The primary refractory group had more pts treated with dual ICI (76 vs. 62%), more pts with poor IMDC risk (29 vs. 19%), and more pts with non-clear cell RCC (27 vs. 19%; all $p < 0.001$). The primary refractory group had shorter diagnosis to treatment interval (mean: 1.6 vs. 2.3 years), lower KPS (median: 80 vs. 90), higher rate of anemia (65% vs. 52%), neutrophilia (11% vs. 9%), and thrombocytosis (30 vs 22%; all $p < 0.001$). The primary refractory group had more liver (24 vs. 17%; $p < 0.001$), bone (39 vs 32%; $p < 0.001$) and lymph nodes metastasis (52 vs. 47%; $p = 0.03$) at the start of 1L therapy. On multivariable analysis, independent factors associated with primary refractory RCC were low KPS, and the presence of liver metastasis or bone metastasis (Table). Dual ICI regimen was associated with a 1.8-fold increase of primary refractory RCC. **Conclusions:** In pts with mRCC, low KPS and the presence of liver or bone metastasis are independent risk factors for the development of primary refractory disease. Primary refractory disease is more commonly observed in pts receiving dual ICI compared to those on ICI+VEGF-TT regimen. Research Sponsor: None.

Multivariable analysis for independent factors associated with primary refractory RCC.

	OR	Lower 95% CI	Upper 95% CI	p-value
Diagnosis to treatment interval < 1 year (yes vs. no)	1.2	0.9	1.6	0.2
Anemia (yes vs. no)	1.37	1.1	1.8	0.03
Low KPS(<80: yes vs. no)	1.9	1.4	2.5	<0.001
Neutrophilia (yes vs. no)	1.3	1	1.8	0.09
Thrombocytosis (yes vs. no)	0.9	0.7	1.3	0.6
Liver metastasis (yes vs. no)	1.7	1.3	2.3	<0.001
Lymph Nodes metastasis (yes vs. no)	1.3	1	1.6	0.07
Bone metastasis (yes vs. no)	1.3	1.03	1.7	0.03
Dual ICI (vs. ICI+VEGF-TT)	1.8	1.37	2.4	<0.001
Non-clear cell RCC (vs. clear cell)	1.3	1	1.8	0.06
Nephrectomy (yes vs. no)	0.9	0.7	1.2	0.6

Long-term clinical outcomes with nivolumab/ipilimumab with or without *Clostridium butyricum* MIYAIRI588 in metastatic renal cell carcinoma (mRCC): A randomized phase Ib clinical trial.

Miguel Zugman, Hedyeh Ebrahimi, Luis A. Meza, Regina Barragan-Carrillo, Xiaochen Li, Marian Llamas-Quitiquit, Joann Hsu, Zeynep Busra Zengin, Daniela V. Castro, Benjamin Mercier, Salvador Jaime-Casas, Alex Chehrazi-Raffle, Jeffrey M. Trent, Peter P. Lee, Motomichi Takahashi, Tanya B. Dorff, Gregory Caporaso, Keehoon Lee, Sumanta Kumar Pal, Nazli Dizman; City of Hope Comprehensive Cancer Center, Duarte, CA; Yale University School of Medicine, New Haven, CT; Translational Genomics Research Institute (TGen), Phoenix, AZ; Miyarisan Pharmaceutical Co., Ltd., Saitama, Japan; Translational Genomics Research Institute (TGen North), Flagstaff, AZ; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In two randomized phase I trials, *Clostridium butyricum* MIYAIRI588 (CBM588), a live biotherapeutic, demonstrated preliminary activity in modulating the gut microbiome, enhancing systemic immune responses, and improving clinical outcomes in patients receiving first-line nivolumab/ipilimumab and nivolumab/cabozantinib for mRCC (Dizman *et al.* and Ebrahimi *et al.* Nature Medicine). Herein, we present the long-term follow-up data for nivolumab/ipilimumab with or without CBM588. **Methods:** Newly diagnosed patients with mRCC, clear cell and/or sarcomatoid histology, and International mRCC Database Consortium intermediate/high risk were randomized to receive nivolumab/ipilimumab with or without CBM588 in a 2:1 ratio. Response outcomes were assessed using RECIST 1.1. Clinical outcomes were secondary endpoints. Objective response rate (ORR; complete response [CR] or partial response [PR]), disease control rate (DCR; CR, PR, or stable disease [SD] $>$ 6 months), progression-free survival (PFS), and overall survival (OS) outcomes were compared across arms. **Results:** Twenty-nine patients were included in the final analysis: 19 in the nivolumab/ipilimumab with CBM588 arm and 10 in the nivolumab/ipilimumab arm. The median age was 66.2 years, 72% were male, 83% had IMDC intermediate risk and 93% had clear cell histology. Baseline characteristics were similar across arms. ORR and DCR were 58% and 79% in nivolumab/ipilimumab with CBM588 arm versus 20% and 20% in nivolumab/ipilimumab arm, respectively (p = 0.06 and p = 0.004). At a median follow-up of 60.0 (95% CI 51.9-68.1) months, the median PFS was 38.2 (95% CI 23.6-52.8) months in the nivolumab/ipilimumab and CBM588 arm versus 19.3 (95% CI 0-41.9) months in the nivolumab/ipilimumab arm (Hazard ratio [HR] 0.24, 95% CI 0.09-0.61 p = 0.003). At the time of data cutoff, 9 (47.4%) and two (20%) patients were alive in the nivolumab/ipilimumab with CBM588 and nivolumab/ipilimumab arms, respectively. The median OS with nivolumab/ipilimumab with CBM588 was 55.0 (95% CI 10.5-75.5) months versus 39.0 (95% CI 23.7-54.3) months with nivolumab/ipilimumab (HR 0.438 [95% CI 0.17-1.1] p = 0.09). **Conclusions:** Although limited by the sample size, the combination of nivolumab/ipilimumab with CBM588 demonstrated superior clinical activity over nivolumab/ipilimumab in our cohort. Additionally, ORR, PFS and OS with nivo/ipi/CBM588 exceeded those observed with nivolumab and ipilimumab in historical datasets (Motzer *et al.* NEJM). Larger efforts investigating the impact of CBM588 on clinical outcomes are underway. Clinical trial information: NCT03829111. Research Sponsor: None.

Vasculogenic mimicry as a potential indicator of drug resistance and prognosis in renal cell carcinoma.

Xingang Cui, Xiuwu Pan, Zichang Liu, Hongfeng Zheng, Wang Zhou; Department of Urology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: Patients with advanced metastatic renal cell carcinoma (RCC) often develop resistance to tyrosine kinase inhibitors (TKIs). Vasculogenic mimicry (VM) refers to the formation of tubular structures by tumor cells mimicking endothelial cells. VM formation is independent of VEGF and endothelial cells, making it inherently resistant to TKIs. Furthermore, hypoxic conditions induced by TKI treatment can promote VM formation, creating a vicious cycle. This study investigates the molecular mechanisms of VM formation and its prognostic significance in RCC. **Methods:** VM incidence in RCC was assessed using PAS/CD31 staining on tissue microarrays. Single-cell sequencing data were used to identify tumor cells undergoing VM differentiation. Cluster analysis was conducted to characterize these cells, and their prognostic value was validated using TCGA data. Pseudotime trajectory analysis and SCENIC algorithms were used to infer their differentiation pathways and identify transcription factors (TFs) regulating VM formation. Tube formation assays were performed for validation. **Results:** PAS/CD31 double staining revealed a VM incidence of 15.87% (10/63) among RCC patients. Notably, VM formation was more frequent in recurrent and TKI-resistant patients, suggesting that VM may serve as a mechanism for TKI resistance. Single-cell data from 11 patients with stages T1a-T3 RCC were analyzed, identifying VM-differentiating tumor cells, termed RCC-VM. GSVA revealed that RCC-VM cells were highly enriched in angiogenesis and EMT-related pathways. GO and KEGG analyses also showed enrichment in angiogenesis pathways. Trajectory analysis of tumor cell subpopulations placed RCC-VM at the terminal differentiation state, suggesting it represents a uniquely differentiated tumor cell type. Using SCENIC, we identified FOSL2 as a key TF regulating RCC-VM differentiation. Knockdown of FOSL2 significantly impaired tube formation in 786-O cells in vitro. Additionally, we identified RCC-VM-specific signature genes (VMDEG) and used Lasso-Cox regression to select four key risk factors (PIM1, MT1G, MT-ND4, DDIT3) to construct a survival risk model. Kaplan-Meier survival analysis demonstrated that patients in the high-risk group had significantly shorter survival times compared to the low-risk group ($p = 0.0013$). The time-dependent ROC curve showed that the model had robust predictive ability, providing potential guidance for personalized treatment of RCC patients. **Conclusions:** Our study highlights VM as a critical mechanism of TKI resistance in RCC, regulated by the transcription factor FOSL2. VMDEG serves as a valuable prognostic marker for RCC patients. Incorporating VM into staging systems such as pT staging and Fuhrman grading may improve risk stratification and treatment planning for RCC patients.
Research Sponsor: None.

4552 Poster Session

Differences in patient characteristics, treatment patterns, and clinical outcomes of renal cell carcinoma patients in public vs private health care systems in Brazil: Insights from the LACOG 1120 registry.

Pablo Barrios, Sabina B. Aleixo, Andrey Soares, Diogo Assed Bastos, Adriano Goncalves E. Silva, Mariane Fontes Dias, Hyrlana Passos, Karine Martins da Trindade, Fernando Sabino Marques Monteiro, Thiago Lins Almeida, Luis Carlos Moreira Antunes, Cristina de Deus Anjos Tavares Sampaio, Poliana Albuquerque Signorini, Tercia Vilasboas Reis, Bruno Santucci, Ricardo Lima Coelho, Manuel C. Maia, Tainá Cabalheiro, Gustavo Gössling, Andre P. Fay; Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; Centro de Pesquisas Clínicas em Oncologia (CPCO) - Hospital Evangélico de Cachoeiro de Itapemirim (HECI), Cachoeiro De Itapemirim, Brazil; Hospital Albert Einstein (HIAE), São Paulo, SP, Brazil; Hospital Sírio-Libanês, São Paulo, Brazil; Instituto do Câncer e Transplante de Curitiba (ICTr), Curitiba, Brazil; Centro de Tratamento de Tumores Botafogo (CTTB) - Oncoclinicas & Co, Rio De Janeiro, Brazil; Santa Casa de Misericórdia de Feira de Santana, Feira De Santana, Brazil; Oncocentro Ceará - Rede D'Or, Fortaleza, Brazil; Hospital Sírio-Libanês, Brasília, Brazil; Hospital Napoleão Laureano - Universidade Federal da Paraiba (UFPB), João Pessoa, Brazil; Universidade Federal de Santa Maria, Santa Maria, Brazil; Clinica Prognóstica - Centro de Pesquisa Clínica Onconeo, Campo Grande, Brazil; Centro Integrado de Pesquisa da Amazônia (CINPAM), Manaus, Brazil; Oncologia D'Or Bahia, Salvador, Brazil; Hemomed Instituto de Oncologia e Hematologia, São Paulo, Brazil; Centro Paulista de Oncologia (CPO) - Oncoclinicas & Co, São Paulo, Brazil and Hospital Adventista de Manaus, Manaus, Brazil; Hospital Porto Dias, Belém, Brazil; PUCRS School of Medicine, Porto Alegre, Brazil and Hospital Nora Teixeira - Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA) and Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

Background: Brazil's dual healthcare system presents unique challenges in addressing disparities in cancer care. Understanding the differences in clinical characteristics, treatment patterns, and clinical outcomes of renal cell carcinoma (RCC) patients (pts) between public and private health systems is crucial for optimizing care. **Methods:** LACOG 1120 Registry collected data from 230 eligible RCC pts across Brazil from Sep. 2022 to Nov. 2023. Patient demographics, tumor characteristics, treatment information, and clinical outcomes were analyzed and stratified by healthcare system (public vs. private). Descriptive statistics and survival analyses were performed using Kaplan-Meier methods. **Results:** 230 pts were included. Median age at diagnosis was 61.0 (52.0–67.0), 65.2% were male, 58.7% white, 26.1% of mixed skin color and 4.3% black. 61.3% were treated in the public system, and 36.5% in the private system. Pts in the public system were more likely to present with advanced disease (stage IV: 25.5% vs. 17.9%) and had a lower proportion of early-stage disease (stage I: 20.6% vs. 33.3%) compared to the private system. Out of 230, 11 (4.8%) received adjuvant treatment, 3 (2.1%) from the public 8 (9.5%) from the private system. Pts from the public system predominantly received adjuvant sunitinib (66.7%) whereas all the 8 pts from the private systems received adjuvant immune checkpoint inhibitor (ICI) (87.5% pembrolizumab, 12.5% nivolumab). First-line treatment for metastatic RCC was given to 34.0% of public and 53.6% of private system pts. Public pts mainly received sunitinib (47.9%) or pazopanib (31.3%), while private pts predominantly received ICIs (42.2%) or ICI-Tyrosine kinase inhibitors (TKI) combos (26.6%). Treatment discontinuation due to toxicity was higher in the public system (40.9% vs. 36.4%). 20.0% and 31.7% of pts were classified as favorable risk in the public and private systems respectively according to IMDC risk criteria. At median follow-up of 41.7 months (95%CI 27.6 - 48.8), median overall survival (OS) from diagnosis was 79.4 months (95% 66.0 - NR). The 5-year (yr) median OS rate differed between systems, 89.6% (95%CI 70.1-90.6) in private and 42.0% (95%IC 31.1-56.7) in public. When stratified by clinical stage (CS), the 2-yr OS for pts with CS I-III was 87% in the public and 96.8% in the private system. For pts with CS IV, the 2-yr OS was 23.8% in the public compared to 60.0% in the private system. **Conclusions:** Significant disparities exist between RCC pts treated in Brazil's public and private health systems, with public system pts presenting with more advanced disease, with restricted access to novel therapies, and experiencing worse clinical outcomes. These findings underscore the urgent need for health policy reforms to address inequities in cancer care access and treatment in Brazil. Research Sponsor: Funding: Ipsen | Sponsor: Latin American Cooperative Oncology Group (LACOG).

4553 Poster Session

Real-world quality of life (QOL) in patients (pts) with metastatic renal cell carcinoma (mRCC) on active surveillance (AS) in the ODYSSEY prospective observational study.

Michael Roger Harrison, Jesse D. Troy, Benjamin L. Maughan, Yousef Zakharia, Elizabeth Marie Wulff-Burchfield, Nrupen Anjan Bhavsar, Yasser Ged, Ajjai Shivaram Alva, Priyanka V. Chablani, Brian Addis Costello, Deepak Kilari, Sorab Gupta, Melyssa Bratton, Muhammad Furqan, Tracy L. Rose, Sarah Jabusch, Kimberly T. Ward, Courtney Page, Tian Zhang, Daniel J. George; Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC; Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Mayo Clinic Arizona, Phoenix, AZ; University of Kansas Medical Center, Kansas City, KS; Department of Surgery, Duke University Health System, Durham, NC; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; University of Michigan Rogel Comprehensive Cancer Center, Ann Arbor, MI; University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; Mayo Clinic Rochester, Rochester, MN; Department of Medicine, Division of Hematology and Oncology, The Medical College of Wisconsin, Milwaukee, WI; Geisinger, Wilkes Barre, PA; Ochsner Health, New Orleans, LA; University of Iowa Hospitals and Clinics, Iowa City, IA; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Duke Clinical Research Institute, Durham, NC; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: AS is a recognized strategy in select pts with mRCC to maximize QOL and delay potential toxicity of systemic therapy (ST); however, only 2 prospective studies of AS in mRCC have been published: only 1 with patient-reported outcomes (PRO) and none in the IO-TKI era. **Methods:** ODYSSEY is a prospective observational study of 500 US pts with mRCC. Eligible pts must have mRCC (any histology), no prior ST, age ≥19. Pts were excluded if treated for non-mRCC cancers or if not followed at a PCORnet study site. Pts completed QOL surveys at baseline, by phone every 3 months for 2 years and then every 6 months until end of follow up. The primary objective is to determine patterns of change in QOL and symptom burden of pts with mRCC. Minimally important differences (MID) are 3 points for FKSI-19 total score, 1 point for the FKSI-Disease Related Symptoms (DRS) subscale and 7 points for FACT-G. Here we report baseline pt characteristics in AS pts compared to ST pts, and baseline QOL differences between these cohorts. **Results:** As of 1/6/25, 392 pts were enrolled of whom 299 were managed with ST, and 93 pts deferred ST; of these, 53 pts (57%) were classified as AS. Pts on AS are median age 68 yrs, 66% male, 94% white, 81% clear cell, 50% favorable risk, 44% intermediate risk. Compared with ST pts, AS pts were more likely to have undergone nephrectomy (91% vs 53%), favorable risk profile (50% vs 15%), pancreatic metastasis (15% vs 5%), and longer time since RCC diagnosis (median 58 vs 3.3 months); and less likely to have bone, brain, or liver metastasis. After median 8.8 months follow-up (IQR 2.9, 16.2), 2 pts (4%) on AS had died compared with 45 pts (15%) on ST. One pt (2%) on AS started first-line therapy and 45 pts (15%) discontinued ST. Mean baseline QOL (FKSI-19 total, DRS and FACT-G) for AS and ST ODYSSEY pts is shown in the Table (higher score indicates better QOL), with RCT data for reference (NA, not assessed). ODYSSEY pts on AS had higher QOL for all measures compared with ODYSSEY pts on ST. FSKI-DRS was the same or lower for pts on AS compared to the pivotal trials, while ODYSSEY pts on ST had both lower FKSI-19 total and DRS. **Conclusions:** In our large prospective cohort from ODYSSEY, pts on AS had higher median QOL scores than pts on ST, but similar to those included in RCTs. These results suggest that some RCT pts could have benefitted from AS. Further follow up is needed to determine long term outcomes in pts on AS and how they respond to deferred ST. Clinical trial information: NCT04919122. Research Sponsor: Bristol Myers Squibb; Exelixis; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.; Pfizer.

Instrument, Mean (SD)	ODYSSEY AS (N=53)	ODYSSEY ST (N=299)	ODYSSEY Difference, AS vs ST (95% CI)	CheckMate 214 (N=425)	KEYNOTE 426 (N=402)	CheckMate 9ER (N=323)	CLEAR (N=351)
FKSI-19 total	63.4 (9.2)	56.3 (12.5)	7.0 (4.0, 10.1)	60.1 (9.8)	NA	58.7 (10.6)	NA
FKSI-DRS	30.8 (4.2)	27.9 (6.0)	2.9 (1.5, 4.7)	30.7 (4.5)	32 (4.2)	30.2 (5.2)	31.3 (4.4)
FACT-G	87.9 (14.0)	82.4 (16.7)	5.6 (1.1, 10.0)	82.6 (15.0)	NA	NA	NA

Machine learning–derived B-cell epitopes classifiers for early detection of renal cell carcinoma.

Thomas Campbell, Colin P. Bergstrom, Christian Remy Hoerner, John Shon, John Leppert, Alice C. Fan; Serimmune, Inc., Goleta, CA; Stanford University School of Medicine, Stanford, CA; Stanford School of Medicine, Stanford, CA

Background: Renal cell carcinoma (RCC) remains a significant cause of cancer mortality in the United States, with poor outcomes for advanced-stage disease and limited tools for early detection. Tumor-specific antibodies, known to develop early in other solid tumors, offer biomarker opportunities for early RCC detection. This study aimed to leverage Serum Epitope Repertoire Analysis (SERA), an advanced platform for profiling B cell epitopes, to develop a machine learning-based classifier capable of distinguishing patients with RCC from those with benign renal masses and from individuals without known renal neoplasms. **Methods:** We obtained 564 serum or plasma samples from 1) 260 patients with pathologically confirmed RCC, spanning all stages; 2) 21 patients with benign renal masses (predominantly oncocytoma and angiomyolipoma); and 3) 283 age-matched non-RCC controls (self-reported healthy donors). The SERA platform uses a library of 8 billion unique 12-mer peptides, each expressed on a DNA-barcoded *E. coli* strain. Number and type of peptides bound by an antibody are identified by next-generation sequencing, enabling comprehensive profiling of B cell epitopes. Using machine learning, a classifier was trained on a subset of 178 samples (88 RCC and 90 healthy controls) to predict the presence of RCC in the validation cohort of 386 samples (172 RCC, 21 benign renal masses, and 193 healthy controls). The area under the receiver operating characteristic curve (AUC) served to evaluate the classifier's performance, overall and stratified by RCC stage. **Results:** Using the SERA platform, 26.4 million potential amino acid motifs were scored based on enrichment in RCC versus controls, yielding 7,244 motifs that met the predefined thresholds for inclusion in the classifier. These features were used to train a 10,000-tree random classification forest. In validation, the model achieved an AUC of 0.76 (95% confidence interval [CI]: 0.72 - 0.81), and scores were not significantly different (Mann-Whitney U test, alpha = 0.05) in the benign renal lesion control samples vs. healthy controls. Performance was consistent across both early- and late-stage RCC, with an AUC of 0.78 (95% CI: 0.70–0.85) for stage 1, 0.72 (95% CI: 0.49–0.95) for stage 2, 0.81 (95% CI: 0.70–0.92) for stage 3, and 0.75 (95% CI: 0.68–0.81) for stage 4 RCC, each compared to controls, demonstrating robust detection across all disease stages. **Conclusions:** Our findings suggest that a non-invasive SERA-based classifier can distinguish RCC from benign renal masses and healthy controls, with consistent performance across all stages of RCC. The robust detection of early-stage RCC underscores the potential of this approach to enhance early diagnosis of RCC and to guide clinical management while obviating the need for renal mass biopsy. Future studies will focus on refining the classifier and validating its performance in larger, multi-institutional cohorts. Research Sponsor: Department of Defense Kidney Cancer Research Program.

Clinical outcomes of patients with primary refractory metastatic renal cell carcinoma receiving second-line (2L) therapies: An International Metastatic Database Consortium (IMDC) study.

Marc Eid, Karl Semaan, Wanling Xie, Razane El Hajj Chehade, Liliana Ascione, David Maj, Martin Zarba, Connor Wells, Lori Wood, Cristina Suárez, Rana R. McKay, Guillermo De Velasco, Jeffrey Graham, Thomas Powles, Neeraj Agarwal, Aly-Khan A. Lalani, Ravindran Kanesvaran, Benoit Beuselinck, Toni K. Choueiri, Daniel Yick Chin Heng; Dana-Farber Cancer Institute, Boston, MA; Arthur J.E. Child Comprehensive Cancer Centre, Calgary, AB, Canada; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; University of California San Diego, Moores Cancer Center, San Diego, CA; Hospital Universitario 12 de Octubre, Madrid, Spain; CancerCare Manitoba, University of Manitoba, Winnipeg, MB, Canada; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; Leuven Cancer Institute, KU Leuven, Leuven, Belgium; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Arthur JE Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: A subset of patients (pts) with metastatic renal cell carcinoma (mRCC) receiving contemporary first line (1L) immune checkpoint inhibitor (ICI) combinations are considered to be primary refractory. The optimal sequence therapy for this patient population is not well established. Herein, we report practice patterns and clinical outcomes of second line (2L) therapy in pts with primary refractory mRCC. **Methods:** Data from pts with primary refractory mRCC to 1L ICI and who received 2L therapy were collected through the IMDC. Patients with primary refractory RCC were defined as patients who experienced progressive disease (PD) as best response per RECIST 1.1 criteria. Overall survival (OS) and time to treatment failure (TTF) were calculated from initiation of 2L therapy; their distributions were estimated by the Kaplan Meier methodology. **Results:** In total, 494 pts had primary progression on 1L ICI, of which 356 (72%) went on to receive subsequent 2L therapy. The most common regimens in the 2L setting included: cabozantinib (n = 137; 38%); sunitinib (n = 115; 32%), and pazopanib (n = 37; 10%). 22% of patients had IMDC poor risk at initiation of 2L. Median follow-up from 2L initiation was 18.8 months. Median OS was 14.5 months, and the median TTF was 5.4 months for the whole cohort. The median OS was 14.4 months (95% CI 11 – 21.4) for cabozantinib, 10.7 months (95% CI 7 -16.6) for sunitinib, and 15.3 months (95% CI 9 – 46) for pazopanib. The median TTF was 4.5 months (95% CI 3.7 -5.6) for cabozantinib, 3.1 months (95% CI 2.8 – 4.4) for sunitinib, and 2.8 months (95% CI 1.7 – 3.6) for pazopanib. The ORR was 20% for pts receiving cabozantinib, 10% for pts receiving sunitinib, and 16% for patients receiving pazopanib. For pts treated with 2L cabozantinib, 84 (61%) had prior dual ICI and 53 (39%) had prior ICI + VEGF. By contrast, for patients treated with sunitinib or pazopanib, the majority (96% and 95%, respectively) had prior dual ICI as 1L. **Conclusions:** To our knowledge, this is the first initiative to report practice patterns and outcomes of subsequent 2L therapies in patients with primary refractory mRCC to contemporary 1L ICI combinations. Cabozantinib was the most frequently used regimen in this patient population and demonstrated favorable clinical outcomes compared to sunitinib or pazopanib. Biomarker evaluation is needed to explore the mechanism of primary resistance and novel therapeutic strategies for this group. Research Sponsor: None.

Outcomes of patients with primary refractory mRCC receiving 2L therapies.

Treatment Arm	N	Median OS, months (95% CI)	Median TTF, months (95% CI)	ORR, %
2L Cabozantinib (1L dual ICI)	84	15 (11 – 26.2)	4.2 (3.4 – 6.6)	20
2L Cabozantinib (1L ICI + VEGF)	53	13.5 (9.8 – NR)	4.8 (3.6 – 5.9)	20
2L Sunitinib	115	10.7 (7 – 16.6)	3.1 (2.8 - 4.4)	10
2L Pazopanib	37	15.3 (9 – 46)	2.8 (1.7 – 3.6)	16

Refining intermediate-risk (IR) stratification in patients (Pts) with metastatic renal cell carcinoma (mRCC) receiving first-line (1L) immunotherapy (IO) within one year of diagnosis (Dx): Findings from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).

Razane El Hajj Chehade, Rashad Nawfal, Karl Semaan, Marc Eid, Eddy Saad, Marc Machaalani, Emre Yekeduz, Clara Steiner, Wassim Daoud Khatoun, David Maj, Martin Zarba, Connor Wells, Sumanta Kumar Pal, Cristina Suárez, Kosuke Takemura, Haoran Li, Sylvan C Baca, Wanling Xie, Daniel Yick Chin Heng, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA; Medical Oncology, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Department of Genitourinary Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; University of Kansas, Lawrence, KS; DFCI/PCC Fellowship Program - Attendings, Boston, MA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: The IMDC risk model is pivotal for predicting clinical outcomes in pts with mRCC, yet variability exists within the IR group. Moreover, therapy initiation within < 1 year post dx, a predominant IMDC risk factor, significantly influences prognosis. Thus, this study evaluates this heterogeneity in IO era, focusing on patients receiving 1L IO within < 1 year post dx. **Methods:** Data from pts with mRCC receiving 1L IO within < 1 year post dx, with IMDC score of 1 or 2, were retrospectively collected from the IMDC. Score 1 pts were defined as those who started treatment < 1 year post dx, while score 2 pts had an additional IMDC risk factor: low hemoglobin (Hb), Karnofsky Performance Status (KPS) < 80, high neutrophil, high calcium (Ca), or high platelet (Plt) count. We assessed overall survival (OS) and time to treatment failure (TTF) using Cox regression, adjusting for age, sex, nephrectomy status, histological type, presence of one or more metastases, and 1L regimen type (IO+IO vs. IO+VEGF). The response was evaluated according to RECIST 1.1 criteria. **Results:** Of the 670 pts initiating 1L IO < 1 year post dx, 331 had an IMDC score of 1, and 339 had a score of 2, subdivided into 5 subgroups as detailed in the table. Pts' median age was 62 years (IQR: 55-69). Median follow-up was 16.6 months. Response rates, 18-month OS, and 6-month TTF rates for each group are shown in the table. Adding the factor of treatment initiation < 1 year post dx, the high neutrophil count has the most significant effect on OS (HR = 4.85, 95% CI: 2.61-9.03, p < 0.001). Also, KPS < 80 significantly affects both OS (HR = 3.93,95%CI = 2.26-6.84), p < 0.001) and TTF (HR = 1.59 95%CI = 1.02-2.61, p = 0.04). Low hemoglobin, as well as high calcium, notably worsen OS without significant impact on TTF. High Plt count shows no significant impact on OS and TTF, possibly due to the low prevalence of this risk factor (15/670). **Conclusions:** Additional risk factors can affect the prognosis of pts with mRCC receiving IO < 1 year post dx. Integrating other biomarkers or radiological features could refine risk stratification, enhancing treatment approaches for IR pts.
Research Sponsor: None.

		% response	18-month OS rate	Adj. HR for OS (95% CI)	6-month TTF rate	Adj. HR for TTF (95% CI)
IMDC=1	Ddx to start ttt<1 year (N=331)	46%	85%	REF	65%	REF
IMDC=2	Dx to start ttt<1 year+ Low Hb(N=255)	37%	73%	1.83(1.33-2.5) p=0.002*	56%	1.04 (1.02-2.48) P=0.66
	Dx to start ttt<1 year+ KPS<80 (N=30)	30%	57%	3.93 (2.26-6.84) p<0.001*	50%	1.59(1.02-2.61) P=0.04*
	Dx to start ttt<1 year+ High Neutrophils (N=22)	9.1%	51%	4.85(2.61-9.03) p<0.001*	41%	1.41(0.86-2.34) P =0.16
	Dx to start ttt<1 year+ High Ca (N=17)	35%	67%	2.68(1.27-5.62) p=0.01*	65%	1.09(0.62-1.93) P=0.75
	Dx to start ttt<1 year+ High plt (N=15)	33%	63%	2.08(0.83-5.23) p=0.11	42%	1.29 (0.69-2.38) P=0.42

Identifying key prognostic indicators in Wilms tumor using machine learning techniques.

Salsabeel Aljawabrah, Sakhr Alshwayyat, Kholoud Alqasem, Tala Abdulsalam Alshwayyat, Abdalwahab M Z M Alenezy, Mustafa Alshwayyat, Noor Almasri; University of Jordan, Amman, Jordan; King Hussein Cancer Center, Amman, Jordan; Jordan University of Science and Technology, Irbid, Jordan

Background: Wilms tumor is a rare pediatric malignancy, accounting for 6% of pediatric tumors and primarily affecting the kidneys. Its impact on quality of life and long-term outcomes complicates management. This study leveraged machine learning (ML) to identify prognostic factors with the aim of enhancing prognosis and survival rates. **Methods:** Data were obtained from the SEER database (2004-2021). Patients who met any of the following criteria were excluded: diagnosis not confirmed by histology, previous history of cancer or other concurrent malignancies, or unknown data. To identify prognostic variables, we conducted Cox regression analysis and constructed prognostic models using ML algorithms to predict the 5-year survival. Patient records were randomly divided into training (70%) and validation (30%) sets. A validation method incorporating the area under the curve (AUC) of the receiver operating characteristic curve was used to validate the accuracy and reliability of the ML models. We also investigated the role of multiple therapeutic options using Kaplan-Meier survival analysis. **Results:** A total of 4,935 children were included. Among them, 47.72% underwent surgery, radiation, and chemotherapy; 45.07% underwent surgery and chemotherapy; and 7.21% underwent surgery alone. Most patients (53.3%) were females, 75% were white, followed by black (16.3%). The mean patient age was 3 years, and the mean tumor size was 10.6 cm. Most tumors were left-sided (51.1%) and 79.8% had no metastasis. The lungs were the most frequent site of metastasis (11%), followed by the liver and lungs at the same time (1.2%), and bone involvement was rare (0.6%). Radical surgery was the most common surgical approach (76.1%), followed by nephrectomy (4.9%). Patients who underwent surgery and chemotherapy had the highest 5-year OS (96.9%) and CSS (96.9%) compared to those who underwent surgery alone (OS: 95.5%, CSS: 95.5%) or surgery with chemotherapy and radiation (OS: 92.9%, CSS: 93.2%). Asian/Pacific Islander and white patients exhibited better OS (94.3% and 95.1%, respectively) than black patients (91.9%). Multivariate Cox regression analysis identified a large tumor size and older age as poor prognostic factors. Gradient boosting and MLP classifiers were the most accurate models. The ML models identified race as the most significant prognostic factor, followed by the TNM stage and age. The performance metrics for all ML algorithms are summarized in Table. **Conclusions:** This is the first study to apply ML to Wilms tumor, effectively identifying key prognostic factors. ML models show promise in enhancing survival predictions, potentially informing personalized treatment strategies, and improving patient outcomes. Research Sponsor: None.

ML Model	Accuracy	Precision	Recall	F1 score	AUC
LR	59.5%	59.5%	99.6%	74.5%	0.573
KNN	56.1%	61.7%	68.7%	65.05%	0.572
RFC	59.9%	61.9%	84.4%	71.4%	0.596
GBC	60.7%	60.5%	97.3%	74.6%	0.582
MLP	60.9%	61.6%	90.5%	73.3%	0.589

Real-world quality of life (QOL) for patients (pts) with metastatic renal cell carcinoma (mRCC) treated with systemic therapy (ST) in the prospective observational ODYSSEY study.

Benjamin L. Maughan, Jesse D. Troy, Yousef Zakharia, Elizabeth Marie Wulff-Burchfield, Nrupen Anjan Bhavsar, Yasser Ged, Ajjai Shivaram Alva, Priyanka V. Chablani, Brian Addis Costello, Deepak Kilari, Sorab Gupta, Melyssa Bratton, Muhammad Furqan, Tracy L. Rose, Sarah Jabusch, Kimberly T. Ward, Courtney Page, Daniel J. George, Tian Zhang, Michael Roger Harrison; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC; Mayo Clinic, Phoenix, AZ; University of Kansas Medical Center, Kansas City, KS; Department of Surgery, Duke University Health System, Durham, NC; Johns Hopkins University School of Medicine, Baltimore, MD; Department of Internal Medicine, Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI; University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; Mayo Clinic Rochester, Rochester, MN; Department of Medicine, Division of Hematology and Oncology, The Medical College of Wisconsin, Milwaukee, WI; Albert Einstein Healthcare Network, Bronx, NY; Ochsner Health, New Orleans, LA; University of Iowa Hospitals and Clinics, Iowa City, IA; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Duke Clinical Research Institute, Durham, NC; Duke University Cancer Institute, Durham, NC; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC

Background: In the past 7 years, 4 immuno-oncology (IO) based combinations have been approved for mRCC. However, QOL data on these combinations are limited to trials in which collection and reporting was not standardized, which further limits cross trial comparisons. Real-world QOL data with multiple treatment regimens are needed to understand how these regimens are tolerated in practice. **Methods:** ODYSSEY is a multi-site, prospective observational study of 500 US pts with mRCC. Pts must have mRCC (any histology), no prior ST, and follow up at a PCORnet study site. Exclusion criteria include treatment for cancer except mRCC. The primary objective is to determine patterns of change in QOL and symptom burden of pts with mRCC. Minimally important differences (MID) are 3 points for FKSI-19 total score, 1 point for the FKSI-Disease Related Symptoms (DRS) subscale and 7 points for FACT-G. **Results:** As of 1/6/25, 392 pts were enrolled of whom 299 were managed with ST. Of pts on ST, 114 were treated with IO-IO, 108 with IO-TKI, 33 with IO alone, 27 with Other, and 18 with TKI alone. Median follow up for all pts is 8.8 months (IQR 2.9, 16.2). IO-IO pts are median age 64 yrs, 81% male, 84% white, 56% prior nephrectomy, 84% clear cell; IO-TKI pts median age 66 yrs, 76% male, 92% white, 43% prior nephrectomy, 66% clear cell; IMDC risk profiles are similar. IO-IO pts are more likely to be KPS 100; whereas, IO-TKI pts have a higher median number of metastatic sites and are more likely to have bone or liver metastasis. With median follow-up of 6.0 (IQR 1.8, 14.9) and 8.8 months (4.5, 17.8) in the IO-IO and IO-TKI cohorts, 17 (15%) and 21 (19%) pts had died with a median time to death of 5.4 (2.5, 6.4) and 5.7 months (4.4, 12.8), respectively. 20 (18%) and 16 (15%) pts on IO-IO and IO-TKI had discontinued therapy at a median of 3.0 (IQR 2.0, 4.0) and 6.4 months (2.4, 13.0), respectively. Rates of discontinuation for disease progression and toxicity are similar. Baseline PROs for pts on ST are shown in the Table (higher score indicates better QOL), with RCT data for reference (NA, not assessed). **Conclusions:** In our prospective multi-center ODYSSEY study, we demonstrate that real world pts treated with contemporary ST have worse baseline QOL than those enrolled on pivotal RCTs. One-third of IO-IO and IO-TKI pts died or discontinued therapy within 6 months of initiation. Our data on real world vs RCT differences in baseline QOL may partially explain the limitations of current IO combination regimens in practice and support development of alternative treatment approaches. Research Sponsor: BMS; Exelixis; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; & Pfizer.

Instrument, Mean (SD)	ODYSSEY IO-IO (N=114)	CheckMate 214 (N=425)	ODYSSEY IO-TKI (N=108)	KEYNOTE 426 (N=402)	CheckMate 9ER (N=323)	CLEAR (N=351)
FKSI-19 total	56.0 (12.5)	60.1 (9.8)	53.8 (11.8)	NA	58.7 (10.6)	NA
FKSI-DRS	27.5 (6.3)	30.7 (4.5)	27.0 (5.8)	32 (4.2)	30.2 (5.2)	31.3 (4.4)
FACT-G	82.4 (16.7)	82.6 (15.0)	78.5 (16.0)	NA	NA	NA

4559 Poster Session

The effect of GLP-1 receptor agonists on outcomes in metastatic renal cell carcinoma patients undergoing immune checkpoint inhibitor therapy: A retrospective multi-institutional US cohort study.

Mohanad Elchouemi, Mostafa Eysha, Mariia Kasianchyk, Arsalaan Asad, Manas Pustake, Ahmed Eysha, Wanyu Zhang, Anna Long, Abdelrahman Yousif; Texas Tech University Health Science Center, El Paso, TX; Texas Tech University Health Science Center El Paso, El Paso, TX; University of Texas Medical Branch John Sealy School of Medicine, Galveston, TX; Texas Tech University Health Sciences Center, El Paso, TX; Al-Azhar University Faculty of Medicine, Cairo, Egypt; Duke University, Durham, NC

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists have played a pivotal role in the management of type 2 diabetes (T2DM). At the same time, immune checkpoint inhibitor (ICI) therapy remains one of the mainstay treatments for metastatic renal cell carcinoma (mRCC). There has been a scarcity of research on the effect of GLP-1 receptor agonists on ICI efficacy in cancer patients. This study presents the first real-world analysis of the effect of GLP-1 receptor agonists on outcomes in mRCC patients receiving ICI therapy. **Methods:** Data was retrospectively collected from TriNetX, a national electronic health record database with 120 million US patients from over 70 healthcare organizations, from 2012-2024. We included patients $\geq$ 18 years old with T2DM and mRCC who underwent ICI therapy. Patients were then stratified into two cohorts: on GLP-1 receptor agonists prior to ICI therapy and not on GLP-1 receptor agonists. Patients in each cohort were then 1:1 propensity score matched (PSM) based on age, sex, race, type of ICI therapy used, comorbidities, other diabetic medications and staging. 1 year outcomes for mortality, major adverse cardiovascular events (MACE) and various immune-related adverse events (irAEs) were reported. **Results:** A total of 2378 patients were identified who met the inclusion criteria. 535 (22%) were in the GLP-1 receptor agonist cohort compared to 2378 (68%) in the non GLP-1 receptor agonist cohort. After 1:1 PSM, 497 patients were in each group. Among both cohorts, 66% were male, 77% white and the average age was about 65 years old. After conducting Cox proportional hazard analyses, GLP-1 receptor agonist use was associated with lower mortality (HR, 0.49 [95% CI: 0.37-0.64]). Moreover, GLP-1 receptor agonist use had lower rates of irAEs, including pneumonitis (HR, 0.61 [95% CI: 0.43-0.85]), hematological complications (HR, 0.78 [95% CI: 0.64-0.95]) and renal complications (HR, 0.67 [95% CI: 0.54-0.84]). There was no significant difference in MACE or other irAEs between the two cohorts. **Conclusions:** Analysis of one of the largest US based databases showed that the use of GLP-1 receptor agonist in T2DM patients with mRCC undergoing ICI therapy, is associated with better overall survival and lower irAES such as pneumonitis, hematological and renal complications. There was no significant difference in MACE. To our knowledge, this is the first study to identify the impact of GLP-1 receptor agonists on the outcomes of mRCC patients undergoing ICI therapy. Further prospective studies are needed to validate these findings and to identify the underlying mechanisms. Research Sponsor: None.

Circulating tumor DNA (ctDNA) monitoring in patients (pts) with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin +/- pembrolizumab (EVP).

Kevin R. Reyes, Tanya Jindal, Beaux Mitchell, Xiaolin Zhu, Chien-Kuang Cornelia Ding, Arpita Desai, Anthony C. Wong, Noah Spector Younger, Daniel H. Kwon, Ivan de Kouchkovsky, Elizabeth Pan, Rahul Raj Aggarwal, Kelly N. Fitzgerald, Carissa E. Chu, Sima P. Porten, Steven Neema Seyedin, Eric J. Small, Terence W. Friedlander, Jonathan Chou, Vadim S. Koshkin; University of California, San Francisco, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; University of California San Francisco, San Francisco, CA; Department of Medicine, Division of Hematology/Oncology, University of California, San Francisco, San Francisco, CA; University of California, San Fransisco, San Francisco, CA; University of California, San Francisco Medical Center, San Francisco, CA

Background: CtDNA is an emerging biomarker in aUC, but its role for pts receiving EVP is unclear. **Methods:** We undertook a retrospective analysis of pts with aUC who were longitudinally tested for ctDNA (MTM/mL) with a tumor-informed assay (Signatera, Natera, Inc) while on treatment (tx) with EV+/-P. Pt data were abstracted from electronic medical record. Outcomes were compared based on changes in ctDNA from pre-tx baseline, using Kaplan-Meier method and Cox proportional hazards test to assess progression-free survival (PFS) and overall survival (OS). **Results:** Longitudinal ctDNA data were available for 36 pts (tx: 28 EV+P; 8 EV). Pts had a median (med) of 3 ctDNA tests (range: 2-14) over 8 months (mos) of med follow-up. At pre-tx baseline, 33/36 (92%) pts had detectable ctDNA. Pt characteristics and outcomes are shown in the Table. After tx start, 26 pts (79%) had a decrease in ctDNA (med time to decrease 50 days), and 11 pts (33%) achieved negative ctDNA (-) after a med of 54 days. The 11 pts with ctDNA (-) had a response rate of 91% (CR: 6, PR: 4, SD: 1). Among 14 pts with ctDNA nadir followed by a rise, 8 pts (57%) had PD on next scan, and med time from initial ctDNA rise to PD was 124 days. Pts who achieved ctDNA (-) within 2 mos of tx (n = 8) had improved PFS relative to pts with ctDNA data (n = 21) who did not (HR: 0.08, 95% CI: 0.01 – 0.59, p = 0.01). Pts with no decrease in ctDNA within 2 mos of tx start (n = 7) had inferior PFS (HR: 5.9, 95% CI: 1.9 – 19.2, $p < 0.01$) and OS (HR: 20.8, 95% CI: 2.3 – 192, $p < 0.01$) vs pts with a ctDNA decrease (n = 22). In the EV+P group, pts with no ctDNA decrease within 2 mos (n = 4) had inferior PFS (HR: 15.9, 95% CI: 1.6 - 154, p = 0.01) vs pts with a decrease (n = 18). **Conclusions:** In this retrospective analysis of pts treated with EV+/-P, 92% had detectable ctDNA and 79% had a ctDNA decrease after tx start. Within 2 mos of tx start, pts who achieved ctDNA (-) had improved PFS, while pts who did not have ctDNA decrease had inferior PFS and OS. These hypothesis-generating results warrant validation in larger prospective cohorts and can inform clinical decision-making. Research Sponsor: None.

	Total cohort (n= 33)	EV+P (n= 25)
Sex – n (%)		
Male	7 (21%)	6 (24%)
Female	26 (79%)	19 (76%)
Primary Tumor Site – n (%)		
Lower Tract	25 (76%)	19 (76%)
Upper Tract	8 (24%)	6 (24%)
Histology – n (%)		
Pure Urothelial	25 (76%)	19 (76%)
Majority Urothelial	7 (21%)	6 (24%)
Majority Variant	1 (3%)	0
Median baseline ctDNA (MTM/mL)		
Responders	23.1	30.1
Non-Responders	39.8	69.6
Outcomes by ctDNA status within 2 mos of EV+/-P tx start,* mos (95% CI), *p		
mOS: ctDNA (-) vs detectable	NR (NR – NR) vs NR (11.7 – NR), p=0.32	NR (NR – NR) vs NR (NR – NR), p= 0.99
mPFS: ctDNA (-) vs detectable	18.7 (NR – NR) vs 7.2 (5.6 – NR), **p=0.01**	NR (NR – NR) vs 7.2 (5.6 – NR), p=0.99
mOS: No ctDNA decrease vs ctDNA decrease	11.7 (3.9 – NR) vs NR (NR – NR), **p<0.01**	NR (3.9 – NR) vs NR (NR – NR), p= 1.0
mPFS: No ctDNA decrease vs ctDNA decrease	3.9 (1.9 – NR) vs 13.2 (7.9 – NR), **p<0.01**	4.8 (1.9 – NR) vs 13.2 (8.4 – NR), **p=0.01**

Avelumab maintenance therapy in patients (pts) with advanced urothelial carcinoma (UC) in Japan: Subgroup analyses by best overall response (BOR) to prior platinum-based chemotherapy (PBC) in a post-marketing surveillance (PMS) population.

Eiji Kikuchi, Masayoshi Nagata, Taito Ito, Masashi Sato, Mie Ogi, Makiko Morita, Masahiro Kajita, Hiroyuki Nishiyama; Department of Urology, St Marianna University School of Medicine, Kanagawa, Japan; Department of Urology, Juntendo University Graduate School of Medicine, Bunkyo-Ku, Tokyo, Japan; Merck Biopharma Co., Ltd., an affiliate of Merck KGaA, Darmstadt, Germany; Research & Development, Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany; Global Development Operations, Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany; Global Patient Safety Japan, Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany; Department of Urology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Background: Avelumab was approved as maintenance therapy for pts with advanced UC that has not progressed after first-line PBC based on results from the JAVELIN Bladder 100 phase 3 trial. Primary analyses of PMS data demonstrated the safety and effectiveness of avelumab maintenance in clinical practice in Japan, consistent with phase 3 results. We report post hoc analyses of PMS data in subgroups defined by BOR to prior PBC. **Methods:** This prospective, multicenter, observational PMS evaluated pts with advanced UC without disease progression after prior PBC who received ≥1 dose of avelumab between Feb and Dec 2021. The observation period was ≤52 wk from the start of avelumab in all pts. Safety assessment was based on occurrence of prespecified adverse drug reactions (ADRs) deemed to be associated with avelumab. Effectiveness outcomes from the start of avelumab maintenance (time to treatment failure [TTF; defined as avelumab discontinuation for any reason] and overall survival [OS]) were estimated using the Kaplan-Meier method. Subgroups were defined by BOR to prior PBC: complete response (CR), partial response (PR), or stable disease (SD). **Results:** The study population included 453 pts from 213 institutions. Median age was 73 y (range, 21-91); 75 pts (16.6%) were aged ≤64 y, 198 (43.7%) were aged 65-74 y, and 180 (39.7%) were aged ≥75 y. Primary tumor site was the bladder in 244 pts (53.9%) and upper tract in 209 (46.1%). Prior PBC regimen was gemcitabine + cisplatin in 267 pts (58.9%) and gemcitabine + carboplatin in 163 (36.0%). BOR to prior PBC was CR in 47 pts (10.4%), PR in 242 (53.4%), and SD in 149 (32.9%). At the end of the observation period, 128 pts (28.3%) remained on avelumab treatment and 184 (40.6%) had received next-line treatment. Median duration of avelumab treatment was 5.1 mo (IQR, 2.3-12.0). Among subgroups defined by BOR to prior PBC, the longest median TTF and highest 1-y OS rate were observed in the CR subgroup; findings were comparable in the PR and SD subgroups (Table). Safety findings were similar across subgroups. **Conclusions:** This PMS population represents the largest prospective observational study of avelumab maintenance therapy in pts with advanced UC in Asia. In post hoc analyses, the safety and effectiveness of avelumab were generally consistent across subgroups defined by BOR to prior PBC. Our findings support the favorable benefit-risk profile of avelumab in clinical practice, irrespective of BOR to prior PBC. Research Sponsor: Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

BOR to prior PBC	All patients (N=453)	CR (n=47)	PR (n=242)	SD (n=149)
Any-grade ADRs, n (%)	144 (31.8)	16 (34.0)	79 (32.6)	45 (30.2)
Grade ≥3 ADRs, n (%)	35 (7.7)	4 (8.5)	16 (6.6)	13 (8.7)
Median TTF (95% CI), mo	4.6 (3.8-5.3)	5.2 (3.4-12.0)	4.6 (3.3-5.7)	4.6 (2.8-5.6)
1-year OS rate (95% CI), %	77.9 (73.7-81.5)	89.4 (76.3-95.4)	76.3 (70.3-81.2)	75.8 (68.0-82.0)

Real-world enfortumab vedotin +/- pembrolizumab (EV+/-P)–based treatment toxicity, treatment discontinuation, and associations with survival in advanced urothelial carcinoma (aUC).

Martin Kurian, Vivek Nimgaonkar, Omar Elghawy, Ronac Mamtani; Hospital of the University of Pennsylvania, Philadelphia, PA; Osler Medical Service, Johns Hopkins Hospital, Baltimore, MD; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: EV-based therapy is central to the standard of care for aUC, increasingly in combination with P. Current understanding of EV-related toxicity is limited to clinical trial data. Here, we use real-world data to characterize the frequency of EV-based treatment-toxicity, -discontinuation, and associations with survival. **Methods:** We performed a post-marketing retrospective cohort study of EV+/-P initiators at the University of Pennsylvania (1/2020-5/2024). The frequency of any of five toxicities (skin reaction, neuropathy, ocular disorder, hyperglycemia, and pneumonitis) and associated treatment-interruptions (hold or discontinuation), -reduction, or -hospitalization were summarized. Among pts with at $\geq$1 year of follow-up, overall survival (mOS) was compared between pts with vs without each toxicity via KM methods. **Results:** Among 123 EV/EV+P treated pts, median age was 68 years, 72% were male, 74% were white, 68% had bladder primary, and 71% treated with EV alone. Frequency of toxicity, time to toxicity, and proportions requiring dose interruption, reduction, and hospitalization are shown (Table). 60% of pts had skin reaction, 47% neuropathy, 28% ocular disorder, 14% hyperglycemia, and 2% pneumonitis; treatment discontinuation occurred among 20% of pts with neuropathy, 5% of those with skin reaction, 3% of those with ocular disorders, and 0% of those with hyperglycemia or pneumonitis. Among 80 pts with at least one-year of follow-up (89% EV monotherapy), mOS was 14.3 months (95% CI: 11.3-19.3). Survival was greater among those with skin reaction, neuropathy, and ocular disorders (mOS skin reaction vs. no reaction: 19.3 vs. 6.4 months, $p < 0.001$; neuropathy vs. no neuropathy: 16.5 vs. 8.2 months, $p = 0.001$; ocular disorder vs. no ocular disorder: 17.1 vs. 11.3 months; $p = 0.001$). **Conclusions:** EV+/-P treatment toxicity occurred in a majority of pts, but treatment discontinuation was infrequent. Presence of toxicity was significantly associated with improved survival. Future work is needed to prospectively validate these findings. Research Sponsor: None.

EV+/-P treatment toxicity and survival outcomes (n=123).

Toxicity	n (% of total)	Months to Occurrence, Median (range)	Dose Held*, n (%)	Dose Reduced*, n (%)	Discontinuation* n (%)	Hospitalization* n (%)	mOS** (n=80)
Skin Reaction	74 (60)	0.7 (0.1-13.8)	33 (46)	33 (46)	4 (5)	4 (5)	19. 3 vs 6.4 (p<0.001)
Neuropathy	58 (47)	2.9 (0.2-9.6)	28 (48)	23 (40)	11 (20)	0 (0)	16.5 vs. 8.2 (p=0.001)
Ocular Disorder	35 (28)	1.8 (0.2-10.6)	4 (11)	3 (9)	1 (3)	0 (0)	17.1 vs 11.3 (p=0.001)
Hyperglycemia	17 (14)	1.4 (0.1-5.6)	5 (29)	0 (0)	0 (0)	0 (0)	9.7 vs. 14.4 (p=0.56)
Pneumonitis	3 (2)	3.8 (3.0-11.0)	1 (33)	0 (0)	0 (0)	1 (33)	22.1 vs. 14.3 (p=0.91)

*n (% of pts w/ toxicity).
**w/ vs w/o toxicity.

Final results of a phase 2 study of HDACi chidamide and PD-1 inhibitor for advanced urothelial carcinoma after platinum therapy.

Zhuowei Liu, Lijuan Jiang, Li Tian, Zhenhua Liu, Zhaohui Zhou, Zhiyong Li, Yanxia Shi, Yunlin Ye, Zikun Ma, Xiangdong Li; 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 Medical Oncology, Sun Yat-Sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: Epigenetic dysregulation is commonly correlated with the pathogenesis and development in urothelial carcinoma. The preliminary results demonstrated that the combination of chidamide (CHI) and tislelizumab (TIS) was well tolerated with clinically meaningful activity in patients (pts) with advanced or metastatic urothelial carcinoma (mUC). Confirmed ORR was 41.7%, median PFS was 4.6 months. Here we present results from the final analysis. **Methods:** Eligible pts aged 18 to 75 years old had recurrend or progressed after platinum-based chemotherapy to assess the efficacy and safety of CHI and PD-1 inhibitor in mUC. All pts received 30 mg oral CHI twice weekly in combination with TIS 200mg Q3W, until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). The secondary endpoints included progression free survival (PFS), disease control rate (DCR), overall survival (OS) , and safety. **Results:** From Jan. 2021 to Oct. 2023, a total of 45 pts were enrolled at Sun Yat-sen University Cancer center. At the data cut-off (Aug, 2024), the median duration of follow-up was 23.2 months (95%CI: 17.2-31.9). Median age was 63 years (IQR: 57-68). ORR and DCR were 44.4% (12CR, 8PR; 95%CI, 29.6-60.0%) and 60% (27/45; 95%CI, 44.3-74.3%), respectively. Median duration of response (DOR) was not evaluable (95%CI, 8.8-NE). Median PFS and OS were 7.0 months (95%CI, 2.4-10.3) and 20.3 months (95%CI, 10.7-NE), respectively. The most common treatment emergent adverse events (TEAEs) included anemia, anorexia, thrombocytopenia, neutropenia, leukopenia, fatigue, hypoalbuminemia. Grade 3 or above TEAEs (≥10%) were neutropenia 24.4%, thrombocytopenia 20.0%, anemia 13.3%.No pts died due to an adverse event attributed to study trearment. **Conclusions:** This study is the first trial to show that combining HDAC inhibitor with PD-1 antibody is a feasible and efficacious novel approach in mUC. Chidamide plus tislelizumab could be a new treatment option in this patient population. Clinical trial information: NCT04562311. Research Sponsor: None.

	CHI+TIS (n=45)
ORR (95% CI), %	44.4 (29.6- 60.0)
CR, %	26.7% (12/45)
PFS	
Median (95% CI), mo	7.0 (2.4-10.3)
36-mo rate (95% CI), %	26.3 (13.4-41.1)
OS	
Median (95% CI), mo	20.3 (10.7-NE)
36-mo rate (95% CI), %	45.9 (28.8-61.4)
DOR	
Median (95% CI), mo	NE (8.8-NE)

Fibroblast growth factor receptor 3 (*FGFR3*) alteration status and outcomes with immune checkpoint inhibitors (ICPI) in patients with metastatic urothelial carcinoma.

Shilpa Gupta, Jessica Lee, Jerry W. Mitchell, Richard Sheng Poe Huang; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Foundation Medicine, Inc., Cambridge, MA; Foundation Medicine, Inc., Boston, MA

Background: The use of immune checkpoint inhibitors (ICPIs) has expanded in the treatment of metastatic urothelial carcinoma (mUC) but response rates are variable, highlighting the need for preditive biomarkers. Tumor mutational burden (TMB) has been previously shown to predict response to ICPI but *FGFR3* alterations are common drivers in mUC and there is preclinical and anectodal evidence that they may predict less favorable outcomes to ICPIs, similar to *ALK* and *ROS1* fusions in lung cancer. We sought to explore the effect of *FGFR3* alterations alone and with TMB on response to ICPI in mUC. **Methods:** 1,416 mUC patients who received hybrid-capture NGS-based genomic profiling were evaluated for their response to ICPI and chemotherapy treatment based on the presence of *FGFR3* alterations (activating point mutations, insertions and deletions, rearrangements) and TMB. The nationwide (US-based) de-identified Flatiron Health-Foundation Medicine mUC clinico-genomic database of NGS results linked to deidentified electronic health record-derived clinical data originating from approximately 280 US cancer clincs (~800 sites of care) was used to assess treatment patterns and real-world overall survival (rwOS) and progression-free survival (rwPFS). Propensity analysis was used to match clinical characteristics between patients receiving first-line ICPI and chemotherapy and included age, disease grade, ECOG, and erdafitinib receipt as features. **Results:** Among 819 patients with mUC who received ICPI, there were no significant differences in rwOS or rwPFS between *FGFR3*-altered (alt; n = 161) and wildtype (wt; n = 658) patients. However, among patients with TMB≥10 mut/Mb, *FGFR3*-alt patients (n = 39) trended towards longer rwOS (20 vs. 14 months, aHR 0.62, 95% CI 0.37-1.02, p = 0.06) and rwPFS (5.5 vs. 4.9 months, aHR 0.66, 95% CI 0.42-1.03, p = 0.07) than *FGFR3*-wt patients (n = 244). Comparing first-line ICPI vs. chemotherapy and adjusting for imbalances, patients with TMB≥10 and *FGFR3*-alts who received ICPI (n = 21) also trended towards longer rwPFS than patients who received chemotherapy (n = 18) (14 vs. 7.1 months, HR 0.55, 95% CI 0.25-1.25, p = 0.2), although no significant difference in rwOS was observed. **Conclusions:** While *FGFR3* status alone is not predictive of response to ICPI, *FGFR3* combined with TMB emerged as a biomarker that may be predictive for response to ICPI in mUC and may have the potential to reconcile differences in previous observations regarding *FGFR3* and ICPI response. Further studies performed with larger patient populations to confirm these findings are warranted. Research Sponsor: None.

4565 Poster Session

Association of tumor-informed ctDNA-based molecular residual disease (MRD) with clinical outcomes for upper tract urothelial cancer (UTUC).

Adanma Ayanambakkam, George Laliotis, Kevin R. Reyes, Beaux Mitchell, Cherry Au, Michael Glover, Margaret F. Meagher, Punashi Dutta, Shruti Sharma, Meenakshi Malhotra, Adam ElNaggar, Minetta C. Liu, Mukti Patel, Sumit Anil Shah, Alan Tan, Vadim S. Koshkin, Tyler F. Stewart; OU Health, Stephenson Cancer Center, Oklahoma City, OK; Natera, Inc., Austin, TX; University of California San Francisco, San Francisco, CA; Rush University Medical Center, Chicago, IL; Stanford University Medical Center, Stanford, CA; UC San Diego Health, La Jolla, CA; Vanderbilt University Medical Center, Nashville, TN

Background: Upper tract urothelial carcinoma (UTUC) accounts for 5–10% of all urothelial carcinomas. Given its aggressive phenotype compared to primary bladder tumors and the lack of efficient biomarkers to guide treatment decisions, disease management remains challenging. Herein, we evaluate the prognostic value of ctDNA-based molecular residual disease (MRD) detection in UTUC. **Methods:** We conducted a retrospective analysis of real-world data from commercial ctDNA testing in a multicenter cohort of patients with UTUC using a personalized, tumor-informed, mPCR-NGS ctDNA assay (SignateraTM, Natera, Inc.). ctDNA was evaluated during the 1) MRD window (2-16 weeks post-surgery, before adjuvant therapy [AT]) and 2) surveillance windows ($>$16 weeks post-surgery if no AT was given or after AT completion). The correlation between ctDNA status and patient outcomes (recurrence-free survival [RFS]) was assessed using Cox regression analysis. RFS was defined as the interval from surgery to the date of radiographic recurrence or any evidence of residual/persistent disease after the completion of surgery or AT. **Results:** A total of 349 plasma samples collected from 45 patients with stages I-IV UTUC between 4/20/2021-12/16/2024 were available for analysis. Neoadjuvant therapy (NAT) was administered for 9% (4/45) of the patients, while 51% (23/45) of patients received AT post-surgery/-diagnosis [chemotherapy 57% (13/23), immunotherapy 39% (9/23), chemoimmunotherapy: 4% (1/23)] and 22% (10/45) received treatment for metastatic disease [EV-immunotherapy or immunotherapy: 40% (4/10), chemotherapy: 40% (4/10), chemo-immunotherapy: 20% (2/10)]. With a median follow-up of 17 (range: 3-71) months, the ctDNA detection rate within the MRD (N = 24) and surveillance (N = 32) windows was 70.8% and 68.8%, respectively. Patients with ctDNA-positivity within the MRD and surveillance windows showed a significantly inferior RFS compared to ctDNA-negative patients (MRD: HR = 13.4, P= 0.012 and surveillance: HR = 14.46, P= 0.01). Notably, ctDNA-positive patients showed a 12-month RFS of 32.1% (95% CI: 11.83–54.6%) and 45.5% (95% CI: 24.4–64.3%), respectively for MRD (N = 17) and surveillance (N = 22) windows, compared to 100% 12-month RFS for ctDNA-negative patients (MRD, N = 7; surveillance, N = 10). Multivariate regression analysis during surveillance revealed ctDNA-positivity as the only factor significantly associated with poor RFS (HR = 17.6, P= 0.011) when adjusted for clinical stage, NAT, and AT. **Conclusions:** This is the first study utilizing longitudinal, tumor-informed ctDNA testing to assess patient outcomes and disease status in UTUC. Our hypothesis-generating results suggest that ctDNA-based MRD detection via tumor-informed ctDNA testing is prognostic of patient outcomes post-surgery in UTUC and warrants further investigation in larger prospective cohorts. Research Sponsor: None.

Targeting the TGFβ signaling pathway to mitigate tumor metastasis in 9p21-loss urothelial bladder cancer.

Cindy Y. Jiang, Yuxue Zhang, Kai Yu, Ying Mei, Wei Qiao, Mohammad Jad Moussa, Jianfeng Chen, Raymond Wang, Jianping Zhao, Amishi Yogesh Shah, Sangeeta Goswami, Charles C. Guo, Arlene O. Siefker-Radtke, Matthew T. Campbell, Linghua Wang, Omar Alhalabi, Jianjun Gao; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, 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; Department of Pathology, 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: We previously identified that 9p21-loss (containing MTAP and CDK2NA genes) occurs in 25% of metastatic urothelial cancer (mUC) and is associated with worse survival and increased visceral metastasis. Additionally, we found significantly increased expression of the TGFβ-SMAD3 pathway in 9p21-loss UC, which is well studied to induce epithelial mesenchymal transition (EMT) and lead to metastasis. We hypothesize that the TGFβ signaling pathway mediates visceral metastasis in 9p21-loss UC. **Methods:** We included mUC patients at MD Anderson Cancer Center (MDACC) who had MTAP testing completed (surrogate for 9p21-loss) and received chemotherapy, immune checkpoint therapy (ICT), and/or antibody drug conjugate between 2012 and 2022. Survival and metastasis were compared between MTAP deficient patients and MTAP proficient patients. The Memorial Sloan Kettering-Metastatic Events and Tropisms (MSK-MET) cohort of mUC patients and IMVigor210 dataset were assessed for genomic alterations. Mouse models bearing CDKN2A-MTAP double knock out (DKO) MB49 tumors and wild type (WT) MB49 tumors, as well as corresponding in vitro models were used for mechanistic studies. **Results:** 298 mUC patients at MDACC were identified with 27% (n = 81) MTAP deficient. MTAP deficient patients experienced significantly worse overall survival (16.2 vs 21.1 months; p = 0.002; HR 1.61; 95% CI 1.2-2.2), progression-free survival (3.9 vs 5.8 months; $p < 0.001$; HR 1.75; 95% CI 1.3-2.4) and increased visceral metastasis (62% vs 39%; p = 0.001) with lung predominance (44% vs 26%; p = 0.003) compared to MTAP proficient patients. We also found in the MSK-MET cohort that 26% (186/714) of patients with mUC to the bladder had lung metastasis and those with lung metastasis had significantly increased frequency of CDK2NA deletion compared to patients without lung metastasis (30% vs 18%; OR 2.0; 95% CI 1.3-3.0). Our preclinical data also demonstrated that CDKN2A-MTAP DKO mice resulted in significantly larger primary bladder tumors and worse survival compared to mice bearing WT MB49 tumors. Additionally, mice bearing orthotopic CDKN2A-MTAP DKO MB49 tumors readily developed lung metastasis. Analysis of the IMvigor210 dataset (N = 298) showed that 9p21-loss UC patients had significantly increased expression of TGFβ and EMT pathway genes. These data are consistent with data from our DKO MB49 tumor models. We are currently assessing the impact of a TGFβ inhibitor on mitigating CDKN2A-MTAP DKO-mediated metastasis. **Conclusions:** Our clinical and pre-clinical data demonstrates that 9p21-loss mUC leads to worse survival and increased visceral metastasis, especially to the lung. We found that the TGFβ signaling pathway may play a role in the development of metastasis. Moving forward, we plan to prospectively investigate the therapeutic potential of TGFβ inhibition in patients with 9p21-loss UC. Research Sponsor: MD Anderson; David H. Koch Center; Joan and Herb Kelleher Charitable Foundation; Williams TNT Fund; NIH/NCI R01; CA254988-01A1; NIH/NCI R01; CA269489-01A1; NIH/NCI R01; CA282282-01.

4567 Poster Session

Phase 1/2 Duravelo-1 study: Preliminary results of nectin-4–targeting zelenectide pevedotin (BT8009) plus pembrolizumab in previously untreated, cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer.

Patrizia Giannatempo, Matthew D. Galsky, Ignacio Duran, Valentina Boni, Andrea Necchi, Antoine Italiano, Meredith McKean, Loic Verlingue, Rama Balaraman, Leslie Robbins DeMars, Kate Josephs, Cong Xu, Oscar Reig Torras; Genitourinary Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milano, Italy; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Department of Medical Oncology, New York, NY; Hospital Universitario Marqués de Valdecilla, IDIVAL Santander, Santander, Spain; NEXT Madrid Universitary Hospital Quironsalud Madrid, Madrid, Spain; Vita-Salute San Raffaele University and IRCCS Ospedale San Raffaele, Milan, Italy; Institut Bergonié, Bordeaux, France; Sarah Cannon Research Institute, Nashville, TN; Centre Léon Bérard, Lyon, France; Florida Cancer Affiliates, Ocala, FL; Bicycle Therapeutics, Cambridge, MA; Hospital Clínic de Barcelona, Barcelona, Spain

Background: Effective and tolerable therapies for patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC) in the first-line setting are needed. Zelenectide pevedotin (zele, previously BT8009) is a highly selective Bicycle Toxin Conjugate (BTC) targeting Nectin-4 and conjugated to MMAE, and has shown an objective response rate (ORR) of 45% and a generally tolerable safety profile as monotherapy in previously treated, enfortumab vedotin-naïve pts with mUC in the ongoing Phase 1/2 study (NCT04561362, Duravelo-1; Reig et al., 2024). Here, we present preliminary data from expansion Cohort B7 of Duravelo-1, investigating zele + pembrolizumab (pembro) in pts with previously untreated, cisplatin-ineligible, la/mUC. **Methods:** Pts who were cisplatin-ineligible by Galsky criteria (Galsky et al., 2011) received zele 5 mg/m^2 on D1, D8, D15 plus pembro 200 mg D1, every 21 days. The primary endpoint was ORR as assessed by investigator per RECIST v1.1. Secondary endpoints included safety and disease control rate (DCR). Treatment-related adverse events (TRAEs) were determined for all pts who received at least one dose of study drugs. **Results:** As of 3 Jan 2025, 22 pts were enrolled from Nov 2023 to Jul 2024 with a median time on treatment of 22.9 weeks and 12 pts still receiving study treatment. Median age was 77 years; 46% of pts had an ECOG performance status (PS) of 2; 55% with CrCl $<$ 60 mL/min. With 20 efficacy evaluable pts, the ORR is 65.0% (95% CI, 40.8, 84.6), including 5 CRs (25.0%; 4 confirmed), 8 PRs (40.0%; 6 confirmed) and 5 SD (25.0%). Median follow-up was 7.1 mo (range 1.0 – 13.2) and median duration of response was not reached. DCR is 90.0%. The most common grade (Gr) ≥3 TRAEs included ALT increased and neutropenia (13.6% each), and diarrhea, asthenia, hypomagnesemia, and pneumonia (9.1% each). Serious TRAEs related to zele or zele + pembro occurred in 9.1%. Treatment-related peripheral neuropathy occurred in 50.0% (27.3% Gr1, 13.6% Gr2, 9.1% Gr3). Other TRAEs of clinical interest included skin reactions (4.5% Gr≥3), hyperglycemia (0.0% Gr≥3), and eye disorders (0.0% Gr≥3). All cases of grade 3 TRAEs of clinical interest were reversible. There were no grade 4/5 TRAEs of clinical interest and no treatment related deaths. **Conclusions:** Zelenectide pevedotin + pembro shows promising anti-tumor activity as a first-line treatment in a cohort of cisplatin-ineligible pts with la/mUC including a large proportion of pts with PS = 2. The combination of zele + pembro was generally tolerable and broadly consistent with the existing safety profiles of each respective agent. No new safety signals were observed with the combination. Zele + pembro combination therapy is being investigated in previously untreated la/mUC pts in the ongoing Phase 2/3 Duravelo-2 study (NCT06225596). Clinical trial information: NCT04561362. Research Sponsor: BicycleTx Ltd.

Real-world analysis of 2IR immune response score in histologic subtype urothelial carcinoma (hsUC).

Jason Robert Brown, Tolulope Tosin Adeyelu, Andrew Elliott, Arnab Basu, Mehmet Asim Bilen, Roger Li, Tyler F. Stewart, Rana R. McKay, Elisabeth I. Heath, Daniel M. Geynisman, Norm Smith, Pedro C. Barata; Division of Solid Tumor Oncology, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; Caris Life Sciences, Phoenix, AZ; University of Alabama at Birmingham, Birmingham, AL; Winship Cancer Institute of Emory University, Atlanta, GA; Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Moores Cancer Center, University of California San Diego, La Jolla, CA; Mayo Clinic, Rochester, MN; Fox Chase Cancer Center, Philadelphia, PA; Caris Life Sciences, Irving, TX; University Hospitals Seidman Cancer Center, Cleveland, OH

Background: The 2IR immune response score was initially developed using bulk RNA sequencing of pre-treatment tissue from ImVigor 210 and CheckMate 275 trials, however these trials enrolled patients (pts) with pure urothelial carcinoma (pUC) histology. Patients with hsUC often exhibit worse response to immune checkpoint inibitors (ICI) than patients with pUC. Here, we evaluated the 2IR score as a prognostic or predictive biomarker in real-world pts with hsUC. **Methods:** Specimens from pts with pUC (n = 1677) and hsUC (n = 417) were profiled at Caris Life Sciences (Phoenix, AZ) using next generation sequencing (NGS) of DNA and RNA. HsUC histologies included majority ($>$ 50%) squamous (n = 340), sarcomatoid (n = 51), neuroendocrine (n = 20), and micropapillary (n = 6) component. 2IR was calculated by comparative RNA expression of 10 adaptive immune genes and 39 pro-tumorigenic genes. Tumors were classified as 2IR-Low (2IR $\leq$ -0.5), -Mid (-0.5 $<$ 2IR $<$ 0), and -High (2IR $\geq$ 0), as previously described (Wang et al., 2022). Spearman correlation analysis was utilized to compare 2IR with tumor mutation burden (TMB), interferon score (IFN) and the tumor microenvironment (TME) cell fractions estimated using quanTIseq. Clinical outcomes included real-world overall survival (rwOS) from ICI start to last contact and time on treatment (ToT) with pembrolizumab, obtained via matched insurance claims data and calculated using Kaplan-Meier methods, while Hazard ratio (HR) was calculated by Cox proportional model. **Results:** For patients with hsUC, distribution of 2IR score was High 5.76%, Mid 33.3%, and Low 60.9%. Median 2IR score was significantly lower in squamous (-0.60, $p < 0.0001$) and sarcomatoid UC (-0.82, $p < 0.0001$) compared to pUC (-0.41) and significantly higher in neuroendocrine UC (-0.15, p = 0.003). Among patients with hsUC, median rwOS was significantly longer for patients with high/mid 2IR score compared to low 2IR score (25.3 [10.9-39.3] months vs. 8.7 [6.2-11.3] months; HR 0.52, 95% CI 0.34 – 0.78, p = 0.0017). ToT with pembrolizumab was also significantly longer for high/mid 2IR score compared to low 2IR score (3.0 [1.4-5.5] months vs. 2.1 [1.4-3.3] months; HR 0.68, 95% CI 0.46-1.00, p = 0.0471). Similar to pUC, 2IR score in patients with squamous UC was positively associated with CD8 T cell infiltration (r = 0.39; $p < 0.0001$), IFN score (r = 0.41, $p < 0.0001$), and TMB (r = 0.20, $p < 0.001$) and negatively associated with M1 macrophage infiltration (r = -0.25, $p < 0.0001$). 2IR scores in hsUC correlated positively but not significantly with mutations in *TP53* (Median: -0.59 vs -0.62, p = 0.067) and *PIK3CA* (Median: -0.56 vs -0.61, p = 0.172) and negatively with mutations in *CDKN2A* (Median: -0.67 vs -0.59, p = 0.052). **Conclusions:** In a real-world cohort of patients with hsUC, we show the 2IR score may be prognostic for rwOS and predictive for pembrolizumab ToT. Prospective studies are needed to further validate this biomarker for use in this population. Research Sponsor: None.

Integrative clinico-genomic evaluation of the human epidermal growth factor receptor 2 (HER2) in urothelial cancer (UC).

Samuel Black, Kai Yu, Mohammad Jad Moussa, Cindy Y. Jiang, Pavlos Msaouel, Funda Meric-Bernstam, Matthew T. Campbell, Linghua Wang, Jianping Zhao, Charles C. Guo, Jianjun Gao, Omar Alhalabi; Department of Medicine, Section of Internal Medicine, Baylor College of Medicine, Houston, TX; 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; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Pathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: HER2-directed therapy with trastuzumab deruxtecan is now FDA approved for UC with high HER2 expression. The interaction between HER2 expression, clinical phenotype and genomic tumor make-up is poorly understood in UC. **Methods:** We reviewed the records of 209 patients with UC and available HER2 expression status treated at MD Anderson Cancer Center between 2021 and 2024. Immunohistochemical (IHC) staining for HER2 and PD-L1 was conducted using 4B5 Ventana PATHWAY and 22C3 pharmDx antibodies, respectively. Formalin-fixed paraffin embedded metastatic or primary UC tumors were sequenced using the MD Anderson Mutation Analysis Precision Panel (MDA MAPP), a 610-gene high-throughput next generation sequencing (NGS) CLIA assay. Chi-square and wilcoxon tests were used to test correlations between HER2 expression and clinico-genomic features. P-values were adjusted for false-detection rate < 0.25. **Results:** We included 209 patients with available HER2 status (see Table). HER2 and PD-L1 had significant inverse correlation (p=0.0062). HER2 3+ status was significantly associated with bladder primary tumors compared to other sites (renal pelvis, ureter, and urethra) (p=0.0261). HER2 expression correlated with *ERBB2* amplifications (0/1+: 0%, 2+: 2%, 3+: 26%, p<0.0001), but not with *ERBB2* mutations. Of 13 patients with *ERBB2* amplification, 12 were HER2 3+, and 1 was HER2 2+. HER2 also correlated with *HELQ* missense mutations (0/1+: 0%, 2+: 0%, 3+: 11%, p=0.0002), *CDK12* alterations (0/1+: 0%, 2+: 0%, 3+: 20%, p=0.0003), and *BCR* missense mutations (0/1+: 0%, 2+: 0%, 3+: 11%, p=0.0002). Of 6 HER2 3+ patients with *CDK12* amplification, all had *ERBB2* amplification. **Conclusions:** Our study confirms prior observations of HER2 inverse correlation with PD-L1, but positive correlation with bladder origin. Beyond the known association with *ERBB2* amplification, we identified molecular correlations between high HER2 expression, missense mutations of *HELQ* and *BCR*, and *CDK12* alterations. The observed co-occurrence of *CDK12* and *ERBB2* amplifications may be related to their proximity (<267 kb apart) on chromosome 17q12. Only 26% of HER2 3+ patients had *ERBB2* amplifications, highlighting the importance of IHC testing, not just NGS testing, to determine therapy candidacy for trastuzumab deruxtecan. Research Sponsor: None.

HER2 Expression Status (n)	0/1+ (105)	2+ (58)	3+ (46)	*p value*
Primary tumor - Bladder, n (%)	74 (70)	43 (74)	**41 (89)**	0.0260
Primary tumor - Other, n (%)	31 (30)	15 (26)	5 (11)	
PD-L1 positive score, median % [IQR]	**6 [1-30]**	**2 [1-10]**	**1.5 [0.75-5]**	0.0062
***ERBB2* amplifications, n (%)**	0 (0)	1 (2)	**12 (26)**	<0.0001
***ERBB2* mutations, n (%)**	10 (10)	8 (14)	9 (20)	0.2030
***HELQ* missense, n (%)**	0 (0)	0 (0)	**5 (11)**	0.0002
***CDK12* amplifications, n (%)**	0 (0)	0 (0)	**6 (13)**	<0.0001
***CDK12* alterations, n (%)**	0 (0)	0 (0)	**9.2 (20)**	0.0003
***BCR* missense, n (%)**	0 (0)	0 (0)	**5 (11)**	0.0002

A real-world picture of biomarker testing in metastatic bladder cancer: A comprehensive assessment of 19,979 patients treated in the US and Europe.

Tiago Costa de Padua, Aime Giorlando, Sheila Mpima, Vicky Casey, Fil Manguid, Diego Esteban, Angela Nunes, Jose Serer, Thomas M. Moehler, Roberto Jorge Bitton; Medical and Scientific Services, Hematology and Oncology Department, IQVIA, São Paulo, Brazil; Data Sciences, Safety and Medical, Hematology and Oncology Department, IQVIA, Buenos Aires, Argentina; IQVIA, Wayne, PA; IQVIA, London, United Kingdom; IQVIA, Madrid, Spain; IQVIA, Lisbon, Portugal; Medical and Scientific Services, Hematology and Oncology Department, IQVIA, Frankfurt, Germany; Medical and Scientific Services, Hematology and Oncology Department, IQVIA, Buenos Aires, Argentina

Background: Recent advances in the molecular characterization of bladder cancer (BC) have led to the development and approval of several targeted therapies in metastatic BC, and biomarker testing is recommended by all guidelines for treatment decision-making. This real-world study aimed to examine patterns of biomarker testing in clinical practice and correlate testing with molecular-guided treatment in patients (pts) with metastatic BC. **Methods:** The IQVIA Oncology Dynamics database, an IQVIA oncology cross-sectional survey collecting anonymized real-world patient-level data from anonymized records of drug-treated cancer pts, was used to identify mBC pts in the US, EU4 (France, Germany, Spain, Italy), and UK from January 2017 to December 2024. We assessed biomarker testing data using descriptive analyzes. **Results:** A total of 19,979 mBC pts were included in this analysis (EU4 + UK: 11,963 pts; US: 8016 pts). FGFR testing has steadily increased over the years in EU4 + UK (from 7% in 2017 to 24% in 2024) and in the US (from 34% in 2019 to 61% in 2024); FGFR alterations were identified in 25.8% of pts in EU4 + UK versus 12.5% in the US. PDL1 testing has also increased over time in both regions; (PDL1 $>$ 10% in 58.9% in EU4 + UK and 57.6% in the US). Microsatellite Instability (MSI) testing and NTRK testing were performed in 12.5% and 8.3% of all pts from EU4 + UK (MSI: 2023-2024; NTRK: 2020-2024). Of these, 24.7% were MSI-high and 5.4% were positive for NTRK alterations. Next Generation Sequencing (NGS) data has been collected since Q1 2022, with an overall testing rate of 9.6% in EU4 + UK and 12.8% in the US. NGS testing has increased in the US over the years (from 3% in 2022 to 65% in 2024). Tumor Mutational Burden (TMB) results are available for pts from EU4 + UK, with TMB $>$ 10 in 55.2% of pts. Regarding the use of targeted therapy, only 230 pts with FGFR3 alterations received any FGFR inhibitors as current or prior treatment, representing 22.9% of positive pts. NTRK inhibitors were used in only 2 pts with positive results (5.7%). **Conclusions:** To our knowledge, this is the largest real-world study evaluating biomarker testing in mBC pts, providing meaningful insights. Our data show an overall low percentage of biomarker testing in clinical practice, but there has been an increase in ordering over the years. Despite the increase, only a limited proportion of patients are treated with targeted therapy, reflecting drug access barriers. We also noted a geographic variation in the positivity rate of FGFR3 alterations, with a higher incidence in patients from EU4 + UK compared to the US. Additionally, the rate of high TMB and positive PDL1 was higher in our data set when compared to historical data; further studies are warranted to better understand these differences. Our study has some limitations, such as the potential for bias and lack of outcome analysis. Research Sponsor: None.

EV-302: Long-term subgroup analysis from the phase 3 global study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (chemo) in previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC).

Jens Bedke, Thomas Powles, Begoña P. Valderrama, Shilpa Gupta, Eiji Kikuchi, Yohann Loriot, Matthew D. Galsky, Srikala S. Sridhar, Evan Y. Yu, Jeannie Hoffman-Censits, Gopa Iyer, Daniel Castellano, Pablo Maroto-Rey, Nataliya Mar, Nancy Ann Dawson, Abhishek Bavle, Seema Rao Gorla, Xuesong Yu, Yi-Tsung Lu, Michiel Simon Van Der Heijden; Department of Urology & Eva Mayr-Stihl Cancer Center, Stuttgart, Germany; Barts Cancer Centre, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, London, United Kingdom; Oncology Department, University Hospital Universitario Virgen del Rocío, Seville, Spain; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Department of Urology, St Marianna University School of Medicine, Kanagawa, Japan; Institut de Cancérologie Gustave Roussy, Villejuif, France; Icahn School of Medicine at Mount Sinai, New York, NY; Princess Margaret Cancer Centre and University of Toronto, Toronto, ON, Canada; Clinical Research Division, Fred Hutchinson Cancer Center; Department of Medicine, Division of Hematology and Oncology, University of Washington, Seattle, WA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; University of California Irvine, Irvine, CA; Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC; Merck & Co., Inc., Rahway, NJ; Astellas Pharma, Inc., Northbrook, IL; Pfizer Inc., Bothell, WA; Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: EV-302/KEYNOTE-A39 (NCT04223856) demonstrated superior efficacy of first-line (1L) EV+P vs chemo and established EV+P as the standard of care (SOC). EV+P is included in global treatment guidelines for patients (pts) with untreated la/mUC. After ≈2.5 years of median follow-up, the benefit of EV+P was sustained; median OS was maintained for > 2.5 years. We present long-term efficacy and safety analyses in the following prespecified subgroups: primary disease site of origin (upper and lower tracts), lymph node (LN)–only disease, and presence of liver metastases (mets) (present and absent). **Methods:** Pts with previously untreated la/mUC were randomized 1:1 to receive EV (1.25 mg/kg; Days 1 and 8; IV) and P (200 mg; Day 1; IV) or chemo (gemcitabine with cisplatin or carboplatin) every 3 wk. Primary endpoints were progression-free survival (PFS) by blinded independent central review (BICR) and overall survival (OS). A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Pts (N = 886) were randomized to receive EV+P (n = 442) or chemo (n = 444) and were analyzed according to the subgroups shown in the Table. At data cutoff (Aug 8, 2024), median follow-up was 29.1 mo (95% CI, 28.5-29.9). PFS by BICR, OS, duration of response, and objective response rate continued to demonstrate sustained benefit of EV+P vs chemo across prespecified subgroups after long-term follow-up (Table). For EV+P, treatment-related adverse events (TRAEs) occurred in 96.0-98.5% and Grade ≥3 TRAEs in 53.4-60.7% of pts across prespecified subgroups, generally consistent with previous reports. **Conclusions:** EV+P continues to demonstrate superior long-term efficacy vs chemo in key subgroups with both favorable and poor prognoses. There were no new safety signals, and AE rates in prespecified subgroups were consistent with the overall population after an additional year of follow-up. This reinforces EV+P as the SOC for the 1L treatment of pts with la/mUC. Clinical trial information: NCT04223856. Research Sponsor: The EV-302 study was funded by Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	Upper tract	Lower tract	LN only	Liver mets present	Liver mets absent
EV+P, n (%)	135 (30.5)	305 (69.0)	103 (23.3)	100 (22.6)	342 (77.4)
Chemo, n (%)	104 (23.4)	339 (76.4)	104 (23.4)	99 (22.3)	345 (77.7)
mPFS, mo					
EV+P	12.3	12.8	22.1	8.1	16.4
Chemo	6.2	6.3	8.3	6.0	6.4
PFS HR	0.542	0.462	0.473	0.548	0.458
(95% CI)	(0.384-0.763)	(0.379-0.564)	(0.317-0.704)	(0.392-0.766)	(0.376-0.557)
mOS, mo					
EV+P	36.5	32.9	NR	19.1	39.3
Chemo	18.3	15.6	24.4	10.1	18.3
OS HR	0.538	0.504	0.512	0.556	0.496
(95% CI)	(0.371-0.781)	(0.408-0.623)	(0.332-0.789)	(0.399-0.776)	(0.400-0.615)

4572 Poster Session

Profiling treatment-associated evolutionary dynamics in advanced urothelial cancer via deep whole exome sequencing of cell-free DNA.

Arvind Ravi, Praful Ravi, Timothy Clinton, Charlene Mantia, Bradley Alexander McGregor, Ilana Bensussen Epstein, Dory Freeman, Brian Danysh, Mendy Miller, Mitra Shavakhi, Aya Abdelnaser, Atish Dipankar Choudhury, Kerry L. Kilbridge, Kent William Mouw, Eliezer Mendel Van Allen, Toni K. Choueiri, David J Kwiatkowski, Joaquim Bellmunt, Gad Getz, Guru P. Sonpavde; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Broad Institute, Cambridge, MA; Broad Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; Bladder Cancer Center, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA; AdventHealth Cancer Institute, Orlando, FL

Background: Monitoring treatment response and identifying resistance mechanisms remain critical challenges in managing advanced bladder cancer. We investigated whether circulating tumor DNA (ctDNA) dynamics and deep whole exome sequencing (D-WES) could provide insights into treatment response and resistance patterns. **Methods:** We prospectively collected blood samples from 70 patients with advanced bladder cancer during treatment. Ultra-low pass whole genome sequencing (ULP-WGS) was performed on 213 plasma samples to quantify tumor fraction, with subsequent D-WES (200X) performed on 47 high-purity (i.e., at least 3% tumor fraction by ichorCNA) samples from 25 patients. Longitudinal analysis of ctDNA levels was correlated with clinical response. Phylogenetic reconstruction for samples in the D-WES cohort was used to identify candidate drivers of therapeutic response and resistance. **Results:** Changes in ctDNA tumor fraction correlated significantly with clinical trajectories: progression (median +1.3%), stable disease (-0.4%, $p = 0.04$ vs progression), and regression (-1.2%, $p = 0.002$ vs progression). Phylogenetic analysis revealed dynamic subclonal competition during treatment response. Mutation burden was significantly elevated in subclones associated with PD-(L)1 response ($p = 0.04$), including within a single patient. A number of novel candidate drivers of therapeutic response were identified across different therapeutic classes, with five genes meeting FDR-adjusted significance ($q < 0.05$): NLGN2, SHANK1 (chemotherapy resistance), GPR56 (taxane resistance), FOSL1, and ORC1L (chemotherapy sensitivity). **Conclusions:** Analysis of ctDNA can effectively monitor treatment response in advanced bladder cancer. D-WES of longitudinal samples revealed novel candidate drivers of therapeutic response and resistance, suggesting distinct molecular mechanisms may govern primary oncogenesis versus treatment response. These findings warrant further investigation in larger cohorts to validate their potential as predictive biomarkers. Research Sponsor: None.

Treatment patterns and clinical outcomes with platinum-based chemotherapy after enfortumab vedotin and pembrolizumab in patients with metastatic urothelial carcinoma.

Michal Sternschuss, Karissa Whiting, Alyssa Arbuiso, Aditi Gupta, Eric Huttenlocher Bent, Nathaniel Alvarez, Ashley M. Regazzi, Stanley Liang, Firas Ahmed, Oguz Akin, Volkan Beylergil, Samuel A. Funt, Dean F. Bajorin, Gopa Iyer, Irina Ostrovnaya, David H. Aggen, Jonathan E. Rosenberg; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Texas Rio Grande Valley School of Medicine, Edinburg, TX; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: Enfortumab vedotin and pembrolizumab (EV/P) emerged as the new standard of care for previously untreated metastatic urothelial carcinoma (mUC), shifting the treatment paradigm. Currently, there are no guidelines for management after EV/P as the outcomes of subsequent systemic treatments, including platinum-based chemotherapy, remain unknown. **Methods:** Our retrospective cohort of patients with mUC treated with EV/P at Memorial Sloan Kettering Cancer Center was reviewed to identify patients receiving subsequent systemic treatments. Clinical data were collected by chart review. Response to EV/P and platinum-based chemotherapy was determined by physician assessment using RECIST v1.1. Progression free and overall survival (PFS, OS) were calculated using the Kaplan-Meier method. **Results:** Of 208 patients treated with EV/P between 10/2018 and 9/2024, we identified 56 patients that received any subsequent systemic treatments. In 68% of patients (n = 38), the initial post EV/P regimen administered was platinum-based chemotherapy. Other therapies included sacituzumab govitecan (n = 6), clinical trials (n = 5), trastuzumab deruxtecan (n = 4), erdafitinib (n = 2) and non-platinum chemotherapy (n = 1). In the 38 patients treated with platinum-based chemotherapy, median age was 74 years, 66% were men, 32% had upper tract primary and divergent histology/subtype component was reported in 47% of cases. One patient had prior platinum exposure (neoadjuvant treatment with rapid metastatic recurrence < 6 months). 16 patients had disease response to EV/P (observed response rate [ORR] 42%, 95% CI 27%, 59%). 36 patients (95%) received doublet therapy with gemcitabine and either cisplatin (n = 7) or carboplatin (n = 29), the two remaining patients received carboplatin/gemcitabine/paclitaxel and carboplatin/etoposide. 7 patients (18%) received maintenance avelumab following platinum. Median follow up was 5 months (IQR: 2.5-6.3). ORR was 50% (95% CI 34%, 66%), including one patient with complete response (CR; 2.9%) and 16 patients with partial response (PR; 47%). Among the patients with CR or PR, median duration of response was 3.8 months (IQR: 2.0-4.6). Median PFS was 4.4 months (95% CI 3.7, 7.8) and median OS was 12 months (95% CI 9.7, 17). **Conclusions:** In a real-world cohort of patients with mUC, platinum-based chemotherapy had substantial antitumor activity after EV/P, although progression-free survival and duration of response were modest. This work provides useful information to further future trial design in the post EV/P setting. Research Sponsor: None.

Disease response with platinum-based chemotherapy after enfortumab vedotin and pembrolizumab.

	N=38 (%)	95% CI
Observed response rate	17 (50%)	34%, 66%
Complete response	1 (2.9%)	0.15%, 17%
Partial response	16 (47%)	30%, 65%
Stable disease	6 (18%)	7.4%, 35%
Progressive disease	11 (32%)	18%, 15%
Unknown	4	

Cutaneous toxicity and clinical outcomes with enfortumab vedotin and pembrolizumab in patients with locally advanced or metastatic urothelial carcinoma.

Alyssa Arbuiso, Michal Sternschuss, Karissa Whiting, Aditi Gupta, Eric Huttenlocher Bent, Nathaniel Alvarez, Ashley M. Regazzi, Stanley Liang, Firas Ahmed, Oguz Akin, Volkan Beylergil, Samuel A. Funt, Dean F. Bajorin, Gopa Iyer, Irina Ostrovnaya, David H. Aggen, Jonathan E. Rosenberg; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: Enfortumab vedotin and pembrolizumab (EV/P) recently became the standard of care frontline treatment for patients with locally advanced or metastatic urothelial carcinoma (la/mUC). In patients treated with EV monotherapy, previous studies reported a potential association between cutaneous toxicities and improved clinical outcomes. While cutaneous toxicities are common with EV/P, the correlation with response has not been described. **Methods:** This is a retrospective cohort of patients treated with first line EV/P for la/mUC at Memorial Sloan Kettering Cancer Center. Clinical data were collected by chart review. Response to EV/P was defined by investigator assessment adhering to RECIST 1.1. Cutaneous toxicity events were recorded and classified as mild (managed with topical agents and/or oral antihistamines) or moderate/severe (requiring further pharmacological interventions and/or dose modifications). Association between clinical characteristics and response were analyzed using univariable and multivariable logistic regression models. **Results:** 186 patients who started EV/P between October 2018 and September 2024 were identified, 166 with distant metastases (89%) and 20 (11%) with locally advanced disease. Median age was 72 years, 68% were male, 31% had upper tract primary, and 44% had subtype/divergent histology component. Rates of bone, lung, and liver metastases were 29%, 24%, and 19%, respectively, and 27% had lymph node only disease. Observed response rate was 64% (119/186; 95% CI 57%, 71%), including a complete response rate of 18% (33/186; 95% CI 13%, 24%). Cutaneous toxicities occurred in 106 patients (57%), predominantly within the first 12 weeks (94/106), 70% of events were classified as mild and 30% as moderate/severe. On univariable analysis, cutaneous toxicity at any time, and before 12 weeks were significantly associated with response to EV/P, with odds ratio (OR) 2.6 (95% CI 1.44 - 4.94, p = 0.002) and 1.91 (95% CI 1.04 - 3.53, p = 0.037). Greater effect was seen based on severity: OR 2.24 (95% CI 1.17 - 4.42, p = 0.017) for mild events and OR 4.12 (95% CI 1.62 - 12.0, p = 0.005) for moderate/severe events compared to patients without cutaneous toxicity. Response to EV/P was less likely with distant metastatic disease (vs. locally advanced; OR 0.28, p = 0.05), and with bone metastases (OR 0.44, p = 0.015), and more likely with lymph node only disease (OR 2.89, p = 0.007). When adjusted for treatment setting (metastatic vs locally advanced) and time on treatment in multivariable analysis, the effect of cutaneous toxicity ≤12 weeks on response was no longer significant (OR 1.7, 95% CI 0.9 - 3.25, p = 0.11). **Conclusions:** In our large, real-world cohort there was a non-significant trend for response to EV/P in patients with cutaneous toxicities. Further studies are needed to define the potential correlation. Research Sponsor: None.

Impact of histological subtypes in patients receiving first-line treatment with enfortumab vedotin/pembrolizumab in advanced metastatic urothelial cancer.

Aya Abdelnaser, Mitra Shavakhi, Arvind Ravi, Ilana Bensussen Epstein, Bicky Thapa, Paloma Galera, Mary-Ellen Taplin, Joaquim Bellmunt; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Medical College of Wisconsin, Milwaukee, WI; Bladder Cancer Center, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Metastatic urothelial carcinoma (mUC) represents a challenging clinical entity with significant morbidity and mortality. Enfortumab Vedotin plus Pembrolizumab (EV+P) has been established as an effective first-line (1L) treatment for mUC, but data regarding the impact of variant subtypes of UC remains limited. This study aims to describe the impact of different histological subtypes on mUC patients (pts) treated with 1L EV+P. **Methods:** This is a single-center retrospective cohort of pts with mUC treated with EV+P in first line between 6/1/2023 and 8/8/2024. Data were collected by chart review, including reviewed pathological reports and their impact on clinical outcomes (ORR, PFS, and OS). Four main histological groups were defined: 1)Transitional UC Predominant: Includes cases where transitional UC is the dominant component. 2) Transitional UC with <50% variant histologies of squamous or glandular differentiation. 3) Transitional UC with >50% variant histologies of squamous or glandular differentiation, including pure squamous or adenocarcinoma types. 4)Other Variant histologies: micropapillary vs. others (plasmacytoid, sarcomatoid, nested, and lipid-rich variants). **Results:** A total of 71 patients with mUC treated with first-line EV+P were included in this analysis, with a median age of 72.78 years. The median follow-up for the cohort was only 8 months (mos). The PFS rate at 12 mos was 43.28%, and the OS rate at 12 mos was 70%. Patients with predominant transitional UC (n=26) had a better response, with an ORR of 57.6% (15/26). Patients with UC having squamous or glandular differentiation (< or> 50%) showed inferior outcomes relative to all other subgroups. Specifically, patients with <50% squamous or glandular differentiation (n=6) had an ORR of 16.6% (1/6), while those with >50% (including pure squamous/glandular) (n=11) showed no response at all (0%, 0/11). Among the rest of the variants, only micropapillary (n=7) showed a substantial benefit with an ORR of 57.1% (4/7). Patients with other variant histologies, including sarcomatoid, plasmacytoid, nested, and lipid-rich (n=8), demonstrated inferior ORRs of 25% (2/8). ORRs based on different histologic subtypes are presented in Table. **Conclusions:** This analysis shows that histological subtypes significantly influence the treatment outcomes of Ev +P treatment. Favorable responses were observed in patients with predominant transitional histologies. Patients with mixed histologies containing squamous or glandular components showed poor responses to EVP independent of the cut-off > or < 50%, raising concern about the validity of the present cut-off value. Adequate responses were observed in the micropapillary subtype only. These findings emphasize the necessity for prospective validation and patient stratification of EV+P treatment in histological subtypes of UC. Alternative treatment strategies should be explored for patients with squamous or glandular subtypes. Research Sponsor: None.

				Variant histologies N=15	
	Transitional UC Predominant) n=37	Transitional UC <50% VH (squamous/ glandular) n=6	Transitional UC >50% VH (squamous/glandular) n=13	Other variant histologies n=8	Micropapillary Variant n=7
ORR	57.6% (15/26)	16.6% (1/6)	0% (0/11)	25% (2/8)	57.1% (4/7)

Assessing treatment outcomes of enfortumab vedotin dose reduction in metastatic bladder cancer.

Hal Difede Rives, Jordan Fredette, Fern Anari, Pooja Ghatalia, Daniel M. Geynisman, Elizabeth R. Plimack, Matthew R. Zibelman; The Fox Chase Cancer Center Foundation, Cheltenham, PA; Fox Chase Cancer Center, Philadelphia, PA; Fox Chase Cancer Center, Temple Health, Philadelphia, PA

Background: Enfortumab Vedotin (EV), an antibody drug conjugate targeting Nectin-4, has emerged as first-line treatment for advanced Urothelial Carcinoma (UC) in combination with pembrolizumab. Acute and cumulative toxicity due to EV can adversely impact quality of life. Treatment related adverse events (TRAEs) are managed with dose and schedule modifications. Current treatment paradigm is to treat until unacceptable toxicity or progression. Our single center, retrospective study, aims to assess the impact of EV dose reduction on treatment duration, AEs, and survival. **Methods:** We conducted a retrospective analysis of patients with UC treated with EV +/- pembrolizumab. Patients were divided into 3 groups: A) 1.25 mg/kg dose and not dose-reduced; B) 1.25 mg/kg dose and dose-reduced; C) EV $<$ 1.25 mg/kg. Data was collected from the EMR and we evaluated OS, PFS, TRAEs, and number of doses received. Kaplan Meier and Cox proportional hazards regression models were used to compare PFS and OS between the 3 groups, and to evaluate treatment dose (1.25 mg or $<$1.25 mg) as a time-varying covariate. TRAEs (y/n) and number of doses received were examined using logistic and negative binomial regression respectively. Regression models adjusted for age, ECOG status, and receipt of concurrent pembrolizumab. **Results:** 153 patients comprised the 3 groups: A) n= 47; B) n=73; C) n=33. The cohort was majority male (78.4%) and white (79.1%) with no significant difference across groups. Median age and ECOG score were both significantly higher in group C ($p<0.001$ and p=0.033, respectively). Overall, 52.9% of patients received prior immunotherapy, while 35.9% of patients received concurrent pembrolizumab (similar across groups). Patients started on full dose EV then reduced (B) had significantly more TRAEs than groups A and C (Neuropathy; A: 15.2%, B:34.2%, C: 12.1%, $p<0.001$; Cutaneous AE; A: 4.3%, B:27.4%, C:2.1%, p=0.004). In unadjusted Kaplan Meier analyses (months), there was a trend but no statistically significant difference in PFS (A:6.4, B:10.1, C:13.1; p=0.1) or OS (A:10.5, B:15.6, C:22.9; p=0.22). In adjusted analyses (minimum 5 doses of EV), there was no difference in total doses received across groups(p=0.6867). Adjusted Cox proportional hazards regression (HR) showed significantly improved PFS and OS for the dose-reduced groups by both landmark (Table 1) and time-covarying analyses ($<$1.25 PFS, HR: 0.6 p=0.032; $<$1.25 OS, HR: 0.59 p=0.039). **Conclusions:** In adjusted analyses dose reduced groups had significantly improved PFS and OS. These results suggest that changes in dose can decrease overall AEs while maintaining efficacy, warranting prospective evaluation. Research Sponsor: None.

	1.25 mg/kg dose and dose-reduced	Significance	Started < 1.25 mg/kg	Significance
Landmark Analyses PFS (HR)	0.48	p=0.019	0.44	p=0.049
Landmark Analyses OS (HR)	0.53	p=0.038	0.47	p=0.063

Pembrolizumab (pembro) with chemoradiotherapy (CRT) as treatment for muscle-invasive bladder cancer (MIBC): Long-term follow up of secondary endpoints of efficacy including overall survival of the PCR-MIB phase II clinical trial (ANZUP 1502).

Andrew James Weickhardt, Farshad Foroudi, Nathan Lawrentschuk, Jing Xie, Yi-An Ko, Mark Sidhom, Abhijit Pal, Peter S. Grimison, Alison Yan Zhang, Siobhan Ng, Colin Tang, Elizabeth Jane Hovey, Colin Chen, George Hruby, Alexander David Guminski, Samantha Richelle Oakes, Ciara Conduit, Ben Tran, Ian D. Davis, Dickon Hayne, Australia and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); Olivia Newton John Cancer Wellness & Research Centre, Austin Health, Melbourne, VIC, Australia; Austin Health, Radiation Oncology, Austin, Australia; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Liverpool Hospital, Blakehurst, Australia; Liverpool Hospital, Liverpool, Australia; Chris O'Brien Lifehouse, Sydney, NSW, Australia; Sir Charles Gairdner Hospital, Perth, Australia; Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; Prince of Wales Hospital, Sydney, Australia; Royal North Shore Hospital, St Leonards, Australia; Royal North Shore Hospital, Sydney, Australia; Australian & New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group, Camperdown, Australia; Royal Hobart Hospital, Hobart, Australia; Monash University and Eastern Health, Box Hill, Australia; UWA Medical School, University of Western Australia, Perth, Western Australia, Australia

Background: We hypothesised pembro could be added without undue toxicity to CRT and would improve efficacy in patients (pts) with MIBC. **Methods:** This multicentre phase 2 trial included people with non-metastatic cT2-T4aN0M0 MIBC (>50% urothelial histology) who declined cystectomy or for whom cystectomy was unsuitable, with no contraindications to CRT or pembro, ECOG performance status 0 or 1, eGFR ≥40 mL/min. Neoadjuvant chemotherapy was not permitted. Pts had maximal TURBT, then whole bladder radiation therapy (RT) (64Gy in 32 daily fractions, mostly IMRT) over 6.5 weeks with weekly cisplatin (35 mg/m^2 IV, 6 doses) and pembro 200mg IV q3wk x 7 doses, both starting with RTx. Surveillance cystoscopy, urine cytology, and CT chest-abdomen-pelvis were performed 12 & 24 weeks after CRT. The primary endpoint was feasibility, determined by a prespecified satisfactory low rate of grade 3-4 non-urinary toxicity, or completion of planned CRT within defined parameters (RT < 7 weeks, >1 cisplatin dose omission). Secondary endpoints include rate of complete cystoscopic response without metastatic disease at 12 & 24 weeks, distant metastases free survival (DMFS), overall survival (OS), and loco-regional progression free survival (LRPFS). Longer term follow up (median 54 months) is presented here from the November 2024 analysis. **Results:** From 2016 – 2021, 28 pts (93% male, median age 72, 96% pure urothelial carcinoma, 29% with carcinoma in situ, 90% pT2) were enrolled at 6 sites. At 48 months, DFMS was 68% (95% CI 46-82%), OS was 64 % (95% CI 42-79%), with median OS not reached (95% CI 25.6m – NE). Local-regional failure free survival at 48 months was 84% (95% CI 63 – 94). Complete response (CR) rate 24 weeks post CRT was 88% (95% CI 70-98%, 23 CR, 3 PD, 2 NE). The The regimen was deemed feasible as previously presented: 6 pts had Gr >3 non-urinary any adverse events (AEs) during treatment or within 12 weeks after completing treatment (2 with delay in RT >7 wks), and 2 pts had cisplatin dose reductions due to G2 AEs. 1 pt had G3 colitis, 1 pt had G2 polymyalgia, 1 pt G2 nephritis. There were no additional immune related adverse events reported with longer follow-up. **Conclusions:** Longer follow up shows promising OS, DMFS and LRPFS with the combination of CRT and pembro for MIBC. There were no new immune related adverse events. Larger randomised trials to test this approach are ongoing. Clinical trial information: NCT02662062. Research Sponsor: Merck Sharp & Dohme LLC (Australia), a subsidiary of Merck & Co., Inc., Rahway, NJ (USA).

Prognostic utility of ctDNA before and after trimodality therapy (TMT) for muscle invasive bladder cancer.

Brendan Raizenne, Vadim S. Koshkin, Suzanne Dufault, Terence W. Friedlander, Julian C. Hong, Carissa E. Chu, Nataliya Mar, Jonathan Chou, Martin Ma, Sima P. Porten, Steven Neema Seyedin; University of California, San Francisco, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; University of California San Francisco, San Francisco, CA; University of California, San Francisco Medical Center, San Francisco, CA; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of California Irvine, Irvine, CA; Department of Radiation Oncology, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: Outside of standard patient and tumor characteristics, biomarkers predicting outcomes after TMT for non-metastatic muscle-invasive bladder cancer (MIBC) are lacking. Tumor-informed circulating tumor DNA (ctDNA) has identified MIBC patients at risk of relapse following radical cystectomy. This study assessed the clinical utility of a ctDNA assay in predicting disease progression following TMT. **Methods:** We retrospectively identified patients (pts) with MIBC (cT2-T4, cN0-N2, cM1) who had TMT between 2019 and 2024 and ctDNA assessment with a personalized, tumor-informed assay (Signatera, Natera, Inc) before and/or after TMT. Standard clinical variables extracted include TNM stage, risk factors at TURBT (carcinoma in situ (CIS) and hydronephrosis) age of diagnosis, primary radiotherapy (RT) dose, chemotherapy regimen/duration, and if elective nodal irradiation (ENI) was received. We analyzed the impact of pre-TMT or post-TMT ctDNA (MTM/mL), as well as changes in ctDNA, on disease-free survival (DFS) using the Kaplan-Meier method. We assessed the impact of ENI on DFS in cN0 pts with positive ctDNA at baseline. Predictors of recurrence were assessed with univariate Cox proportional hazard models. **Results:** Among 34 pts, median age was 69 (interquartile range (IQR) 62-79), majority were male (91%), had cT2 (73.5%), were cN0 (85%), had no CIS (76%) or hydronephrosis (94%). The median dose of RT was 64 Gy. Ten (29%) patients had detectable ctDNA prior to TMT. Median follow-up was 13.2 months from last RT dose of TMT. Pts with detectable ctDNA after TMT had inferior DFS compared to pts with persistently undetectable (pre/post-TMT) or pts with ctDNA clearance (median survival of 5 months vs 15 and 19 months, respectively, log-rank p = 0.056). Table 1 shows results for predictors of DFS after TMT. Pts with detectable ctDNA post-TMT (n = 4) all developed distant metastatic recurrence. Local recurrences did not present with a detectable ctDNA following TMT. Pts with measurable ctDNA at baseline demonstrated potentially prolonged DFS after ENI (n = 4) compared to the non-ENI cohort (n = 6), but did not meet statistical significance (7.6 months vs not reached, p = 0.2). **Conclusions:** Persistently detectable ctDNA following TMT correlates with disease-free survival. Larger cohorts are needed to assess role of ENI in pts with detectable ctDNA prior to TMT. These results are hypothesis-generating and should be validated prospectively. Research Sponsor: None.

Predictors of DFS after TMT.

	HR (95% CI)	P-value
Histologic type (Reference (Ref) group: Pure urothelial)		
Urothelial with minor variant	0.76 (0.21-2.84)	0.69
CIS on TURBT (Ref group: No CIS)		
CIS	0.61 (0.16-2.28)	0.46
Pre-TMT Hydronephrosis (Ref group: No Hydronephrosis)		
Hydronephrosis	3.63 (0.77-17.19)	0.1
Response of ctDNA status to TMT (Ref group: Detectable to Detectable)		
Detectable to Undetectable	0.12 (0.02-1.00)	0.05
Undetectable to Undetectable	0.26 (0.04-1.75)	0.17

Quantifying patient preferences for bacillus Calmette-Guérin (BCG) and PD-(L)1 inhibitors in high-risk non-muscle invasive bladder cancer (NMIBC): A discrete choice experiment.

Pam Hallworth, Anthony Eccleston, Brad Mason, Brett Hauber, Bethany Bell, Josh Coulter, Lisa Marin, Allison Thompson, Joe Jones, Jane Chang, Lara Ayala-Nunes, Julia Brinkmann, Carys Guest, Adam Gater, Abin Koshy, Joseph C Cappelleri, Stephanie Chisolm, Raj Satkunasivam; Adelphi Research, Bollington, United Kingdom; Pfizer Ltd, Surrey, United Kingdom; Adelphi Values Ltd, Patient-Centered Outcomes, Bollington, United Kingdom; Pfizer Inc., New York, NY; Adelphi Research, Doylestown, PA; Pfizer Pharma GmbH, Berlin, Germany; Pfizer Inc., Groton, CT; Bladder Cancer Advocacy Network (BCAN), Bethesda, MD; Department of Urology, Houston Methodist Hospital, Houston, TX

Background: Intravesical Bacillus Calmette-Guerin (BCG) induction + maintenance (I+M) is the standard of care for high-risk NMIBC. Disease recurrence and progression is common. The studies investigating programmed cell death-1/programmed death-ligand 1 (PD-[L]1) inhibitors + BCG aim to enhance treatment outcomes and reduce burden in BCG naïve high-risk NMIBC. There is limited evidence on patient preferences for these combination regimens. **Methods:** A discrete choice experiment quantified preferences for attribute levels related to BCG and PD-(L)1 inhibitors. Attributes and levels were informed by a literature review, patient interviews, regulatory scientific advice, clinical experts and a patient advocate. Patients completed hypothetical choice tasks describing administration mode and frequency for PD-(L)1 inhibitors and BCG (induction [I]; I+M), median event-free survival (EFS) and adverse events (AEs: bladder AEs; chronic endocrine conditions; serious immune AEs). Hierarchical Bayesian modelling estimated preference weights (PWs) for attribute levels. PWs identified level combinations with the lowest choice probability. Relative importance (RI) was calculated by systematically varying attribute levels and capturing the gain in choice probability. **Results:** 150 patients (77 BCG-naïve; 73 BCG-experienced) in the United States completed the survey. Clinician-confirmed diagnosis (17%) and/or self-reported ongoing or planned BCG I+M (99%) was obtained. The sample was 51% male, had a median age of 63 years (49-74) and diverse by race (Caucasian 46%; African American/Black 27%; Other 27%) and ethnicity (Hispanic/Latino/Spanish 21%). EFS was the most important attributes to patients (RI 17.2), followed by bladder AEs (RI 16.4) and serious immune AEs (RI 14.0). Administration attributes were important (RI 9-9.9), but less important than other attributes. PWs show that short duration ($<$ 1 minute) subcutaneous (SC) injections was the most preferred PD-(L)1 route and shorter BCG schedule was preferred. **Conclusions:** Findings highlight the value of prolonging EFS, effective clinical management of BCG AEs and reducing administration burden in future BCG + PD(L)1 regimens. Research Sponsor: Pfizer Inc.

Attribute	Level	Mean PW	95% CI (±)	RI*(%)
EFS (months)	36	3.46	0.28	17.2
	27	-1.03	0.11	
	22	-2.43	0.22	
Bladder AEs (%)	0	2.98	0.29	16.4
	35	-0.10	0.12	
	75	-2.88	0.26	
Serious immune AEs (%)	0	1.40	0.22	14.0
	10	-0.09	0.09	
	20	-1.31	0.18	
Chronic endocrine conditions (%)	0	0.99	0.15	12.6
	5	-0.08	0.08	
	10	-0.91	0.16	
PD-(L)1 frequency (weeks)	6	0.45	0.10	9.9
	4	-0.10	0.10	
	3	-0.35	0.06	
PD-(L)1 administration route and time	SC <1 minute	0.15	0.09	9.5
	SC 7-10 minutes	0.06	0.10	
	IV 30-60 minutes	-0.21	0.08	
BCG schedule	I	0.25	0.14	9.0
	I+M	-0.25	0.14	

*Sums to 88.7. The remaining 11.3 corresponds to an attribute used for analysis only.
CI: confidence interval; IV: intravenous infusion.

Evaluation of surrogate endpoints in muscle-invasive bladder cancer (MIBC): A systematic review and meta-analysis.

Matthew D. Galsky, Yu Wang, Allison Thompson, Heidi Wirtz, Priyam Patel, Eleni Theodorou, Vanessa Shih, Jennifer Uyei, Devon J Boyne; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Department of Medical Oncology, New York, NY; IQVIA, San Francisco, CA; Pfizer Inc., New York, NY; Pfizer Inc., Bothell, WA; Astellas Pharma Europe, Addlestone, United Kingdom; Formerly Pfizer Inc., Bothell, WA; IQVIA, Inc., San Francisco, CA

Background: Overall survival (OS) is the gold-standard efficacy measure in oncology; however, it can take several years for OS data to mature, particularly in the clinically localized setting in patients undergoing curative intent treatment. To accelerate patient access to novel therapies, surrogate endpoints can be used to accelerate the assessment of new treatments when an early measure is reasonably likely or known to predict the clinical benefit for a target outcome such as OS. MIBC is a potentially curative disease with a complex and evolving treatment landscape involving radical cystectomy with or without systemic therapies, and bladder sparing strategies. Despite the need for surrogate endpoints in MIBC, there is limited research on their validity in this patient population. **Methods:** This study evaluated the trial-level surrogacy of event-free survival (EFS), progression-free survival (PFS), and disease-free survival (DFS) with respect to OS in MIBC. A systematic literature review (SLR) was conducted to identify randomized controlled trials (RCTs) that evaluated anti-cancer treatments (neoadjuvant, adjuvant, perioperative, and bladder sparing therapies) in MIBC and reported results for OS and ≥1 surrogate endpoint of interest. Studies published between Jan 1, 2000 and Jun 26, 2024 were identified by searching the MEDLINE, EMBASE, and CENTRAL databases. Grey-literature sources included recent conference proceedings and clinical trial registries. Study quality was assessed using the Cochrane Risk of Bias v2 tool. Data from studies with comparable outcome definitions for EFS, PFS, and DFS were combined into a broad composite outcome definition (cEFS). Trial-level surrogacy between the hazard ratio (HR) for cEFS and OS was evaluated. Analyses were conducted using a weighted linear regression (WLR) model and the bivariate Daniel & Hughes (D&H) model. Measures of surrogacy included the Pearson correlation coefficient (r) to measure the strength of association and the surrogate threshold effect (STE) to estimate the minimum HR for cEFS needed to reliably predict a HR for OS < 1. **Results:** 32 RCTs across 71 publications were included in the SLR; 14 were included in the cEFS analyses based on a feasibility assessment. Trials with a high-risk of bias (n = 1) or that evaluated the initiation of systemic therapy after disease progression (n = 4) were excluded. The HR for cEFS was strongly correlated with the HR for OS (r = 0.94; 95% CI: 0.72-0.99). Based on the STE, a HR <0.88 for cEFS would be needed to reliably predict a HR < 1 for OS. Results from the D&H model were consistent with these findings. **Conclusions:** These results suggest that at the trial level, the HR for cEFS is highly correlated with the HR for OS in MIBC across various treatment settings. cEFS may assist clinicians, regulatory agencies, and reimbursement bodies in contextualizing the benefits of novel treatment strategies in MIBC. Research Sponsor: Pfizer; Astellas Pharma Inc.

4581 Poster Session

MRI radiomics to predict outcome of neoadjuvant chemotherapy in patients with muscle invasive bladder cancer undergoing radical cystectomy.

Lawrence Howard Schwartz, Oguz Akin, Samuel Gold, Yufei Deng, Alfonso Lema-Dopico, Stephanie Chahwan, Josip Nincevic, Lisa Ruby, Marinela Capanu, Aditya Apte, Jonathan E. Rosenberg, Alvin C. Goh, Amita Dave; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering, New York, NY; Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cisplatin-based neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) is the standard of care in patients with muscle-invasive bladder cancer (MIBC). Although the administration of NAC for MIBC has increased over the years, it still does not meet actual patient's needs, particularly in cT2 BC, for which it is currently recommended in clinical guidelines. Indeed, with the development of new cytotoxic and targeted therapies, large ongoing prospective studies have been designed to test their efficacy either alone or in combination in the neoadjuvant setting. Multidisciplinary management is critical in this disease setting; including advanced imaging to assess response to treatment and outcome correlations. Despite the promising applications of radiomics in MIBC treatment outcome assessment, challenges remain, including successful harmonizing of imaging data, which impacts the consistency of radiomic features. The objective of the study is to assess the ability of radiomic features extracted from a robust magnetic resonance imaging (MRI) processing pipeline to predict the outcome of NAC prior to RC in patients with MIBC. **Methods:** A total of 105 MIBC patients (67M/38F), median age (65), clinical stage 2 (77), 3(28)) who were treated with NAC (cisplatin-based therapy) and underwent RC were included in this study. All patients underwent preNAC MRIs using the standard acquisition protocol. Tumors were segmented on T2w, T1w, and post contrast-T1w images by GU radiologists. To standardize MRI intensity values across scans, preprocessing steps were required to ensure comparability between patients. After N4-bias field correction of image intensities, images were standardized to robust z-scores using median and mean absolute deviation of intensities within respective regions of interest. IBSI-compatible pyCERR software was used to extract radiomics features. A total of 289 radiomic features, including shape, first-order statistics, and higher-order textures, were analyzed for the overall survival (OS, time between RC to death) as an outcome. To identify features associated with OS, we trained an Elastic Net Cox regression model for each MRI sequence, with performance evaluated by concordance index (c-index) on a 30% held-out test set. **Results:** The same shape feature (major axis length) from post contrast-T1w and T2w images was selected as important by the elastic net with test set c-index of 0.55 [0.42 – 0.67) and 0.56 [0.42 – 0.70], respectively. Kaplan-Meier method further confirmed the significance of this feature ($p < 0.05$) for OS risk stratification, using the median feature value as the cutoff point. **Conclusions:** The study demonstrated the value of radiomics in predicting survival to NAC with MIBC which can be further validated with a larger independent cohort. MRI radiomics may be an additional tool for prognostication. Research Sponsor: None.

4582 Poster Session

Distinct genomic landscape of Lynch syndrome–associated urothelial cancer.

Jussi Nikkola, Lauri Ryyppö, Juuso Vuorinen, Lauri Moilanen, Maarit Ahtiainen, Kirsi Pylvänäinen, Hanna Selin, Tuomo Virtanen, Matti Nykter, Thea Veitonmäki, Jukka-Pekka Mecklin, Toni T. Seppälä, Matti Annala; Department of Urology, Tampere University Hospital, Tampere, Finland; Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Centre, Tampere, Finland; Department of Pathology, Hospital Nova of Central Finland, Jyväskylä, Finland; Department of Education and Research, The Wellbeing Services County of Central Finland, Jyväskylä, Finland

Background: Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by DNA mismatch repair (MMR) deficiency and associated with a 10–25% lifetime risk of urothelial cancer (UC), particularly in the upper urinary tract. We aimed to investigate the somatic genomic landscape of LS-associated urothelial cancer (LS-UC) using targeted and whole-exome sequencing (WES). **Methods:** We analyzed 41 surgical tumor samples accrued to five Finnish biobanks between April 1987 - June 2022 and 3 urine DNA samples from 34 LS-UC patients, all enrolled in the Finnish Lynch Syndrome Registry. Tumors were profiled using the UroScout assay, targeting 25 UC-associated genes, to identify somatic mutations. Immunohistochemistry was performed to assess MMR protein loss, and WES was conducted on selected cases to investigate the broader mutation landscape. A comparative analysis of the genomic and mutational landscapes in LS-UC versus sporadic UC was performed. **Results:** We show that telomerase reverse transcriptase (*TERT*) promoter mutations found in 83% of sporadic UC are almost completely absent (5%) in LS-UC ($p < 0.00001$). Instead, all LS-UC exhibited a 5-methylcytosine deamination (CG > TG) and microsatellite instability driven mutation landscape, characterized by highly frequent *ARID1A* (82%), *FGFR3* (80%), and *KMT2D* (78%) mutations, as well as preferential usage of CG > TG mutation hotspots. We propose that scarcity of *TERT* promoter mutations in LS-UC is due to inability to create the GABP binding motif 5'-GGAA through CG > TG mutation or microsatellite instability. Additionally, many mutation hotspots recurrently mutated in sporadic UC were not present in LS-UC. **Conclusions:** Our findings establish LS-UC as a distinct disease entity with a unique genomic signature driven by constrained hypermutation. Our proposed explanation that *TERT* mutations are absent in LS-UC due to constrained hypermutation is supported by our discovery that other UC driver genes also exhibit an altered mutation landscape in LS-UC. These insights advance the understanding of LS-UC tumorigenesis and support the development of tailored diagnostic and therapeutic approaches for this patient population. Research Sponsor: Jane and Aatos Erkko Foundation; Academy of Finland Center of Excellence Program; Finnish Cultural Foundation; Finnish Medical Foundation; Orion Research Foundation; Sigrid Juselius Foundation; Relander Foundation; Cancer Society Finland; iCAN Precision Medicine Flagship of the Academy of Finland; Competitive State Research Funding of Tampere University Hospital.

Study EV-103 cohort H: Neoadjuvant treatment with enfortumab vedotin (EV) monotherapy in cisplatin (cis)-ineligible patients (pts) with muscle invasive bladder cancer (MIBC)—3-year efficacy results.

Nataliya Mar, Daniel P. Petrylak, Christopher J. Hoimes, Jonathan E. Rosenberg, Thomas W. Flaig, Theodore Stewart Gourdin, Pedro C. Barata, Elizabeth Henry, Mehmet Asim Bilen, Saby George, Santosh Rao, Vasileios J. Assikis, Earle F Burgess, Brian E. Lewis, Sandy Srinivas, Seema Rao Gorla, Changting Meng, Yalin Zhu, Peter H. O'Donnell; University of California Irvine, Irvine, CA; Yale Cancer Center, New Haven, CT; Duke Cancer Institute, Durham, NC; Memorial Sloan Kettering Cancer Center, New York, NY; Division of Medical Oncology, Colorado University School of Medicine, Aurora, CO; Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; University Hospitals Seidman Cancer Center, Cleveland, OH; 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, Atlanta, GA; Levine Cancer Institute, Charlotte, NC; Tulane University, New Orleans, LA; Stanford University Medical Center, Stanford, CA; Astellas Pharma, Inc., Northbrook, IL; Pfizer Inc., Bothell, WA; University of Chicago, Chicago, IL

Background: For cis-ineligible pts with MIBC undergoing radical cystectomy and pelvic lymph node dissection (RC+PLND), no neoadjuvant treatment options have been shown to improve survival, highlighting a clinical need. EV previously demonstrated encouraging antitumor activity in cis-ineligible pts with MIBC as neoadjuvant treatment in EV-103 Cohort H. We present updated 3-year efficacy results. **Methods:** EV-103 Cohort H enrolled cis-ineligible pts with MIBC (cT2-T4aN0M0) and ECOG PS ≤2 who were eligible for RC+PLND. Pts received neoadjuvant EV monotherapy (1.25 mg/kg) on Days 1 and 8 every 21 days for 3 cycles before undergoing RC+PLND. Primary endpoint was pathological complete response (pCR) rate by central pathology review. Secondary endpoints included event-free survival (EFS) per investigator assessment (INV), OS, and safety. A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Overall, 22 pts were enrolled. 86.4% of pts completed all 3 cycles of neoadjuvant EV treatment. Three pts (13.6%) discontinued neoadjuvant EV due to AEs. All pts underwent RC+PLND; 13 (59.1%) were in long-term follow-up at data cutoff (Nov 20, 2024). Median follow-up was 49.7 mo (range, 3.1-53.6). pCR rate was 36.4% (8/22; 95% CI, 17.2-59.3). Median EFS by INV was 40.1 mo (95% CI, 14.5-NE) for all pts, NR (95% CI, 6.5-NE) for pts with pCR, and 18.8 mo (95% CI, 6.7-NE) for pts without pCR. Estimated EFS rate by INV at 24 and 36 months was 62.0% (95% CI, 38.2-78.9) and 56.9% (95% CI, 33.4-74.8), respectively, and improved in pts with pCR. Median OS was NR (95% CI, 33.4-NE) in all pts. Estimated OS rate at 24 and 36 months was 77.3% (95% CI, 53.7-89.9) and 68.2% (95% CI, 44.6-83.4), respectively. Key updated 3-year efficacy data are shown in the Table. The safety profile was consistent with prior reports, and no new safety concerns were seen. **Conclusions:** Based on 3-year efficacy results, neoadjuvant EV monotherapy treatment continued to show encouraging antitumor activity in cis-ineligible pts with MIBC, including median EFS and OS exceeding historical real-world data in cis-ineligible patients following RC alone (Li Eur Urol Oncol 2024; Rose SESAUA 2023). The safety profile was generally manageable and consistent with the known AE profile of EV in other settings. Phase 3 trials evaluating perioperative EV + pembrolizumab in cis-eligible and -ineligible pts with MIBC (KN-905/EV-303, KN-B15/EV-304) are ongoing. Clinical trial information: NCT03288545. Research Sponsor: The EV-103 study was funded by Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

Median EFS by INV (95% CI), months	
All pts	**40.1 (14.5-NE)**
pCR	**NR (6.5-NE)**
Non-pCR	**18.8 (6.7-NE)**
3-year EFS rate by INV (95% CI), %	
All pts	56.9 (33.4-74.8)
pCR	72.9 (27.6-92.5)
Non-pCR	46.4 (19.3-69.9)
Median OS (95% CI), months	NR (33.4-NE)
3-year OS rate (95% CI), %	68.2 (44.6-83.4)

n=22. Median values should be interpreted with caution due to small sample size.

Revolutionizing bladder cancer follow-up: Personalized urinary ctDNA analysis for detecting minimal residual disease.

Xuebin Wan, Zikuan Zhang, Jiaman Teng, Shifu Chen, Dongwen Wang; HaploX Biotechnology Co., Ltd., Shenzhen, China; Cancer Hospital Chinese Academy of Medical Sciences, Shenzhen Center, Shenzhen, China; HaploX Biotechnology Co., Ltd, Shenzhen, China

Background: As one of the most common malignant neoplasms of the urinary tract, bladder cancer (BC) has received widespread attention with respect to high incidence and tend to recur and progress. Circulating tumor DNA (ctDNA) serves as a valuable tool for detecting and monitoring minimal residual disease (MRD). Here, we conducted a prospective study to assess the potential of urinary ctDNA (utDNA) as a biomarker for measuring MRD in patients for non-muscle-invasive bladder cancer (NMIBC). The objective of this study was to evaluate the utility of longitudinal utDNA in informing adjuvant therapy decisions, enhancing clinical monitoring strategies, and ultimately improving BC prognosis. **Methods:** A total of 67 patients diagnosed with stage I-IV BC were recruited for the study from 2022.11 to 2024.12. For each patient, a customized panel was developed and synthesized, encompassing up to 45 baseline mutations, including SNVs and Indels. In addition to the patient-specific panel, a standardized core panel targeting hotspot regions was incorporated. Whole exome sequencing (WES) was conducted on cancer tissue samples and blood leukocytes in order to reduce the risk of false-positive findings and to exclude potential germline mutations, respectively. **Results:** The study cohort consisted of 59 patients diagnosed with BC, 7 patients with renal pelvis cancer, and 1 patient with ureteral cancer. 59 individuals, accounting for 88% of the sample, had a median age of 65 years. UtDNA was identified in 64 out of 67 preoperative patients, resulting in a detection rate of 95.5%. Furthermore, the correlation between urine samples and tissue samples was confirmed by Pearson's correlation analysis, yielding a correlation coefficient of ($r = 0.31$). 10 patients (14.9%) experienced a recurrence following TURBT. Residual tumors were detected in 7 of the recurrent patients who tested positive for urinary utDNA, accounting for 70% of the cases (7/10). Notably, the presence of positive utDNA in urine samples was observed 3 to 8 months prior to any indications on imaging studies. Monitoring of MRD demonstrated a consistent reduction in utDNA concentrations following surgery. Among patients with complete remission (CR), 9 individuals who initially tested positive for MRD post-surgery subsequently tested negative. **Conclusions:** The findings revealed a high level of concordance between the mutations identified in the tumor and those detected in the utDNA. Patients with positive utDNA exhibited a greater risk of cancer recurrence compared to those who tested negative for utDNA. Urine-personalized MRD detection strategies are anticipated to enhance the efficacy of adjuvant therapy and improve prognostic assessments in patients with BC. None. Clinical trial information: ChiCTR2400079704. Research Sponsor: None.

4585 Poster Session

An exploratory study of clostridium butyricum combined with neoadjuvant chemoimmunotherapy in urothelial carcinoma.

Xiao Yang, Qiang Cao, Lingkai Cai, Juntao Zhuang, Hao Yu, Zhengye Tan, Qiang Lyu; Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; First Affiliated Hospital of Nanjing Medical University, Nanjing, China; The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Neoadjuvant chemoimmunotherapy using gemcitabine, cisplatin, and anti-PD1 has shown survival benefits for advanced bladder cancer patients, though response rates remain low. Recent studies highlight the role of clostridium butyricum in anti-tumor immunity, but its potential to enhance bladder cancer therapy is unexplored. **Methods:** This exploratory study (NCT06696742) involved patients with cT2-T4aN0M0 urothelial carcinoma at First Affiliated Hospital of Nanjing Medical University. Participants were randomized into two groups, one received with GC+anti-PD1 (gemcitabine 1.0 g/m^2 D1 and D8, cisplatin 70 mg/m^2 D2-4, and tislelizumab 200 mg D8 once every 21 days for 3-4 cycles), and the other received the same regimen plus Clostridium butyricum tablets (1-2 tablets, three times a day). Primary observations were pathological complete response (pCR, ypT0) and pathological down-staging ($<$ ypT2), the second observations included imaging assessment (RECIST 1.1) and safety. **Results:** In the combination group, 23 out of 30 patients completed treatment and underwent radical cystectomy, achieving a clinical complete response (CR) rate of 52.2% (12/23) and a partial response (PR) rate of 39.1% (9/23). Two patients (8.6%) showed stable disease (SD) and seven patients are still receiving treatment. Pathological downstaging was observed in 82.6% (19/23) of the patients, with 52.2% reaching ypT0 (12/23). In the control group, all 26 enrolled patients completed treatment and underwent radical cystectomy. The clinical CR rate was 30.7% (8/26), while the clinical PR rate was 42.3% (11/26). Six patients (23.1%) had stable disease, and 1 patient (3.8%) experienced disease progression (PD). Pathological downstaging occurred in 61.5% (16/26) of the patients, with 26.9% (7/26) achieving ypT0. The combination group demonstrated significantly higher rates of clinical CR+PR (P = 0.037) and pathological downstaging (P = 0.042) compared to the control group. There was no statistical difference between the two groups in terms of demographic characteristics. **Conclusions:** Combining neoadjuvant chemoimmunotherapy with Clostridium butyricum improves pathological and clinical response rates in cT2-T4aN0M0 urothelial carcinoma patients. Clinical trial information: NCT06696742. Research Sponsor: None.

Updated efficacy and safety results from ReBirth, a phase II study of risk-based bladder-sparing therapy for MIBC.

Yijun Shen, Xiaolin Lu, Xuejun Ma, Wei Liu, Dingwei Ye; Department of Urology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Cancer Hospital, Xuhui, Shanghai, China

Background: Trimodal therapy (TMT) has achieved long-term survival and persistent oncologic control in selected MIBC patients, however, tailored treatment based on chemotherapy plus PD-1 inhibitor responses is currently absent. Furthermore, the safety and efficacy of hypofractionated radiation in combination with PD-1 inhibitors and concurrent chemotherapy is worth exploring. **Methods:** This was a two-stage, single-arm, phase II trial recruiting cT2-4aN0-1M0 MIBC pts. Based on results of cystoscopy, urine cytology and imaging after first stage (Tislelizumab (T) 200 mg on D1, Cisplatin (C) 70 mg/m^2 on D1 and Gemcitabine (G) 1000 mg/m^2 on D1 and D8 Q3W for 3-4 cycles), pts achieving cCR (cT0, cTa) were treated with T, while the other pts received T and chemoradiotherapy (whole bladder 44Gy/16 fractionation combined with C as radiosensitizer, if lymph node was positive, it could be dosed to the maximum tolerable dose, such as tumor boost 11Gy/4 fractionation). The primary endpoint was 1-year bladder-intact event-free survival (BI-EFS) rate in the intention to treat (ITT) population (from enrolment to muscle-invasive recurrence, nodal or distant metastasis, radical cystectomy (RC) or death). Secondary endpoints included 1-year BI-EFS rate in the per-protocol (PP) population, metastasis-free survival, recurrence-free survival and safety. **Results:** As of January 16, 2025 (median follow up: 14.3 months), 32 pts with a median age of 64 (36-79) years were enrolled (cT2: 71.8%; cT3: 21.9%; cT4: 6.3%; cN1: 6.3%). One pt withdrew consent and were not evaluated for efficacy. In the ITT population, 22 (71.0%) pts achieved cCR and 9 (29.0%) pts were non-cCR. Four pts underwent RC before finishing the first-stage treatment. 1-year BI-EFS rate was 86.9% (95%CI, 68.8-94.9) in the ITT population and 95.8% (95%CI, 73.9-99.4) in the PP population. In the PP population, 1-year BI-EFS rate for cCR pts and non-cCR pts was 100% and 80% respectively. Overall, 5 pts had T1HG recurrence. Meanwhile, 3 pts developed distant metastases (Bone:3; distant lymph node:2). TRAEs of any grade were found in 78.1% pts and 42.3% experienced grade 3-4 TRAEs. No new safety signs were discovered. **Conclusions:** The updated findings continued to show promising efficacy and manageable toxicity via the two-stage treatment. Non-cCR pts might avoid RC through intensified treatment with chemoradiotherapy and T. Follow-up for long-term survival outcomes is still ongoing. Clinical trial information: NCT05531123. Research Sponsor: None.

4587 Poster Session

Postoperative assessment using urinary tumor DNA (utDNA) to identify potential candidates for repeat transurethral resection of bladder tumor (re-TURBT) in non-muscle invasive bladder cancer (NMIBC): A retrospective analysis.

Zihan Xue, Yunkai Qie, Hailong Hu, Chong Shen, Rongjiang Li, Renhao Chen, Jingwen Han, Yuda Lin; The Second Hospital of Tianjin Medical University, Tianjin, China; The Second Hospital of Tianjin Medical University, Tianjin, Tianjin, China

Background: The role of routine repeat transurethral resection of bladder tumor (re-TURBT) in managing non-muscle invasive bladder cancer (NMIBC) remains controversial, especially when the initial resection includes the detrusor muscle. Urinary tumor DNA (utDNA) seem really promising in urothelial carcinoma diagnosis and detection of minimal residual disease. Here, we investigated the correlation between post-initial TURBT utDNA results and the pathology of secondary resection to assess utDNA's potential for precisely identifying patients who may benefit from re-TURBT. **Methods:** A retrospective analysis was conducted on patients with HG Ta/T1 bladder carcinoma (BCa) who underwent re-TURBT in 2 to 6 weeks after initial TURBT at The Second Hospital of Tianjin Medical University between 2020 and 2024. All visible tumor were completely resected and detrusor muscle was collected at the initial surgery. Urine samples were collected and utDNA analysis was performed using a validated next-generation sequencing (NGS) platform a week after initial TURBT. The secondary resection includes the base of the primary tumor, resection margins, excision scar and any suspicious lesion. The results of utDNA testing were compared with the histopathology from re-TURBT. **Results:** 130 patients met the study inclusion criteria. Re-TURBT was successfully performed in all study participants. Urinary tumor DNA test was positive in 39 patients; of whom 35 (89.7%) showed positive repeat biopsy (HR = 7.42, 95%CI = 2.94-18.67, $P < 0.001$). The sensitivity, specificity, positive and negative predictive value of utDNA test for re-TURBT histopathology were 76.1% (95%CI : 64-88) , 95.2% (95%CI : 91-99) , 89.7% (95%CI : 80-99) , 87.9% (95% CI : 81-95) , respectively. On a median (range) follow-up of 23 (3-47) months , 15 cases of tumor recurrence were encountered in 14 (10.7%) patients. On multivariate Cox regression analysis, the post-initial-TURBT utDNA test was significantly associated with tumor recurrence (HR = 4.48, 95%CI : 2.0-9.8, $P < 0.001$). **Conclusions:** Our findings suggest that utDNA analysis after initial TURBT can effectively identify patients with residual disease who are likely to benefit from re-TURBT and that utDNA is an independent predictor of tumor recurrence. This non-invasive liquid biopsy method has the potential to identify beneficiaries of re-TURBT, and optimize the management of HG Ta/T1 bladder cancer. Further prospective studies are warranted to validate the clinical utility of utDNA in this setting. Research Sponsor: None.

Updated results from a phase II study of perioperative disitamab vedotin (RC48-ADC) plus cadonilimab (AK104) for HER2-expressing muscle-invasive bladder cancer (MIBC).

Sujun Han, Feiya Yang, Yong Zhang, Xiongjun Ye, Hongzhe Shi, Bolin Jia, Xingang Bi, Wasilijiang Wahafu, Hongsong Bai, Linjun Hu, Xin Wang, Nianzeng Xing; Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Department of Urology, National Cancer Center & National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, General Internal Medicine, Beijing, China; Cancer Hospital of HuanXing ChaoYang District Beijing, Beijing, China; Oncology, Shanxi Cancer Hospital, Taiyuan, China; Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: Several current ongoing clinical trials have shown promising efficacy and safety of antibody-drug conjugates (ADCs) alone and in combination with immune checkpoint inhibitors (ICIs) as neoadjuvant treatment for patients with MIBC (ASCO 2024). Disitamab vedotin (RC48-ADC) is a novel humanized anti-HER2 ADC. RC48-ADC combined with cadonilimab (AK104), known as the PD-1/CTLA-4 bispecific antibody ICI, may have enhanced synergistic anti-tumor effects attributed to the mechanism of action and achieve more clinical benefit. Here, we report updated results from a phase II study of perioperative RC48-ADC plus AK104 in HER2-expressing MIBC (NCT06074484). **Methods:** This single-arm, open-label, multicentre study evaluates the efficacy and safety of RC48-ADC plus AK104 as a novel neoadjuvant and adjuvant therapy in patients (pts) with treatment-naïve HER2-expressing (immunohistochemistry, IHC 1+, 2+, 3+) MIBC (T2-T4a, N0-1, M0; ECOG PS score 0-1). Eligible pts received neoadjuvant RC48-ADC (2.0 mg/kg D1 Q2W, 4 cycles) + AK104 (6.0 mg/kg D1 Q2W, 4 cycles) followed by radical cystectomy and pelvic lymph node dissection (RC+PLND), and postoperative adjuvant RC48-ADC (2.0 mg/kg D1 Q3W, 6 cycles) + AK104 (10.0 mg/kg D1 Q3W, 14 cycles). The primary endpoint was pathologic complete response (pCR, pT0N0M0). Secondary endpoints were pathologic downstaging rate (pDS, ypâ‰¤T1N0), disease-free survival (DFS), overall survival (OS), objective response rate (ORR), and safety. **Results:** By January 2025, 43 pts had been successfully enrolled. Of these, 81.4% (35/43) were male and 18.6% (8/43) were female, with a median age of 65 years (range, 44-78). HER2 expression was positive (IHC 2+ or 3+) in 72.1% of pts and PD-L1 positive (CPS ≥ 10) in 34.9%. The pCR rate was 64.71% (22/34, 95% CI, 47.85-78.58) in all evaluable pts, 81.82% (9/11) in HER2 1+ and 56.57% (13/23) in HER2 2+/3+ pts, meanwhile 77.78% (14/18) in cT2, 30.00% (3/10) in cT3, and 83.33% (5/6) in cT4a/N1 pts. The overall pDS rate was 76.47% (26/34). Treatment-related adverse events (TRAEs) of any grade occurred in 90.7% of pts (39/43), with ≥ Grade 3 TRAEs in 18.6% (8/43), including fever, rash, bone marrow hypocellular, alanine aminotransferase increased, and immune-mediated myocarditis or pneumonitis. No Grade 4 or Grade 5 TRAEs occurred. At a median follow-up of 11.3 months (95% CI, 9.0-12.1), 2 pts had died, but the median DFS and OS were not reached which remained stable on study and would be updated. **Conclusions:** Neoadjuvant and adjuvant RC48-ADC plus AK104 demonstrated favorable efficacy and a manageable safety profile, supporting its potential as a valuable treatment modality for HER2-expressing MIBC. Long-term benefits and further understanding the role of this combination therapy in the perioperative setting of MIBC will be critical to advance treatment strategies. Clinical trial information: NCT06074484. Research Sponsor: RemeGen; Akesobio.

4589 Poster Session

Microbiota proteomics profiles in muscle-invasive bladder carcinoma related to response to neoadjuvant chemotherapy.

Alvaro Pinto, Fernando Becerril-Gomez, Lucía Trilla-Fuertes, Eugenia García-Fernández, Jorge Pedregosa-Barbas, Francisco Zambrana, Imanol Martinez, Pablo Gajate, Rocio Lopez Vacas, Gustavo Rubio, Ricardo Ramos-Ruiz, Sandra Nieto-Torrero, Pedro Lalanda Delgado, Ana Pertejo, Jonas Grossmann, Antje Dittmann, Carlo Bressa, María Pilar González-Peramato, Juan Angel Fresno-Vara, Angelo Gámez-Pozo; Oncology Department, Hospital La Paz Institute for Health Research-IdiPAZ, Hospital Universitario La Paz, Madrid, Spain; Molecular Oncology Lab, INGEMM, University Hospital La Paz - IdiPAZ, Madrid, Spain; Pathology Department, University Hospital La Paz - IdiPAZ, Madrid, Spain; Medical Oncology Department, University Hospital La Paz - IdiPAZ, Madrid, Spain; Hospital Universitario Infanta Sofía, San Sebastian De Los Reyes, Spain; Medical Oncology Department, University Hospital Fundación Jiménez Díaz, IIS-FJD, Madrid, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Infanta Sofía University Hospital, San Sebastián De Los Reyes, Spain; Genomics Unit, Parque Científico de Madrid, Madrid, Spain; IdiPAZ Biobank, La Paz University Hospital-IdiPAZ, Madrid, Spain; Molecular Oncology Lab, University Hospital La Paz - IdiPAZ, Madrid, Spain; Proteomics Unit, Functional Genomics Center of Zurich, Zurich, Switzerland; Functional Genomics Center Zurich, University of Zurich / ETH Zurich, Zurich, Switzerland; Francisco de Vitoria University, Madrid, Spain; Molecular Oncology Lab, University Hospital La Paz-IdiPAZ, Biomedical Research Networking Center on Oncology-CIBERONC, ISCIII, Madrid, Spain

Background: Muscle-invasive bladder carcinoma (MIBC) poses significant challenges due to high recurrence and mortality rates, coupled with the toxicity of neoadjuvant chemotherapy (NACT). This has driven the search for biomarkers to improve treatment management and patient quality of life. **Methods:** Fifty-eight FFPE samples from MIBC patients obtained from transurethral resection (TURBT) were studied. Microbiota analysis was performed by amplification and sequencing of the V4 variable region of the 16S rRNA gene and using Qiime2 software for taxonomic identification. Proteins were extracted and digested from TURBT samples and analyzed by mass spectrometry with data-independent acquisition. For protein identification, a reference database was built, including both the human proteome and bacteria genera proteomes identified by 16S experiments. Proteomics data were processed with Perseus and analyzed using probabilistic graphical models (PGMs) and hierarchical clustering. **Results:** We have information about treatment response for 56 patients. Twenty-four patients achieved a pathological complete response (43%), with a median disease-free survival of 22 months, and a median overall survival of 29.23 months. 151 bacteria genera identified by 16S experiments, were included in the metaproteomics database. In proteomics experiments, 42 bacteria and 5,111 human proteins were identified. After applying quality criteria, 13 bacteria proteins were used for the subsequent analyses. Hierarchical clustering analysis identified three groups with different microbiota protein profiles: Microbiota1, Microbiota2 and Microbiota3. These groups showed significant differences in response to NACT. A higher proportion of non-responders (73%) vs. responders (27%) was observed in Microbiota2 compared to the other groups (54% in Microbiota1 and 36% in Microbiota2), whereas a predominance of responders (64%) was observed in Microbiota3 (46% in Microbiota1 and 27% in Microbiota2) (p= 0.0481). In a previous work, our group defined three proteomics-based groups related to response to NACT (Layer1 (1.1, 1.2 and 1.3)) (Pinto et al., SEOM 2024). Significant differences were also observed in the distribution of Layer1 between the microbiota clusters. Microbiota2 had a higher representation of patients belonging to Layer1.3, characterized by a majority of non-responders and Microbiota3 had a higher proportion of patients from Layer1.1. **Conclusions:** To our knowledge, this is the first metaproteomics study in FFPE samples from bladder carcinoma patients for biomarker discovery. Three distinct microbiota protein profiles were identified, one with higher proportion of non-responders. The potential role of these bacteria in NACT response needs further study, highlighting metaproteomics as a promising avenue for biomarker development. Research Sponsor: None.

Efficacy and safety of disitamab vedotin (RC48) combined with toripalimab as adjuvant therapy after radical surgery for patients with HER2-overexpression upper tract urothelial cancer (UTUC): A single-arm, prospective, phase 2 clinical trial.

Shouyong Liu, He Miao, Song Xue, Feng Xu, Zhenyu Xu, Dian Fu, Haowei He, Wenquan Zhou, Jingping Ge, Le Qu; Department of Urology, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China; Department of Urology, Jinling Hospital, Clinical School of Medical College, Nanjing University, Nanjing, China

Background: UTUC is rare and highly aggressive. The prognosis is poor, especially for high-risk patients, even after radical surgery. Adjuvant chemotherapy is the standard therapy, but with limited efficacy, indicating a need for more effective regimens. RC48, an anti-HER2 antibody-drug conjugate, combined with toripalimab, an anti-PD-1 monoclonal antibody, has shown promising results in locally advanced or metastatic urothelial carcinoma (C014 trial). We evaluate the efficacy and safety of RC48 combined with toripalimab as adjuvant therapy for patients with HER2 IHC 2+/3+ UTUC after radical surgery. **Methods:** This is a single-arm, prospective, phase 2 clinical trial (NCT05917158). Eligible criteria were patients with histologically confirmed HER2 IHC 2+/3+ UTUC after radical surgery and were staged as T2-4NanyM0 or TanyN1-2M0, with no prior neoadjuvant therapy. The intervention was intravenous RC48 (2 mg/kg) combined with toripalimab (3 mg/kg) triweekly for 6 cycles, followed by toripalimab (3 mg/kg) triweekly for up to 1 year. The primary endpoint was DFS, and the secondary endpoints were OS, safety, and MRD analysis. **Results:** 45 patients (35 males [77.8%], median age 68 years [IQR 58-71]) were enrolled. The patients were staged as: 43 (95.6%) in II, 1 (2.2%) in III, and 1 (2.2%) in IV. All patients were HER2-overexpression (80% in IHC 2+, 20% in IHC 3+). 25 patients (55.6%) met cisplatin-ineligibility. By the data cutoff date on January 14, 2025, the median follow-up time was 12.2 months (IQR 6.7-17.6). 4 relapses occurred: 2 in lymph nodes, 1 in the prostate, and 1 in lymph nodes and the bladder. The 1-year DFS rate was 90.0%, and the median DFS has not been reached. All patients experienced treatment-related adverse events (TRAEs). The most common TRAEs were hypoesthesia (51.1%), increased blood glucose (48.9%), anemia (46.7%), increased creatinine (46.7%), and hypertriglyceridemia (46.7%). TRAEs of grade ≥3 occurred in 20% of patients. 8.9% of patients experienced immune-related adverse events, including rash and hypothyroidism. Among the patients, 16 (35.6%) completed treatment, 19 (42.2%) were still undergoing intervention, 4 (8.9%) discontinued therapy due to TRAEs: 1 with hypoesthesia, 1 with lymphocytopenia and hypoesthesia, 1 with nausea, vomiting, and decreased appetite, and 1 with pruritus and diarrhea, and 2 withdrew after completing 4 cycles of combined regimen due to personal reasons. No deaths occurred during the follow-up period. **Conclusions:** This is the first prospective clinical trial evaluating the efficacy and safety of the new adjuvant regimen for patients with HER2-IHC 2+/3+ UTUC. It showed promising DFS outcomes and a manageable safety profile, highlighting its potential as a new adjuvant therapy in patients with HER2-IHC 2+/3+ UTUC. Clinical trial information: NCT05917158. Research Sponsor: None.

First survival outcomes and biomarker results of SURE-01: Neoadjuvant sacituzumab govitecan (SG) monotherapy, followed by radical cystectomy (RC), in patients with muscle-invasive urothelial bladder cancer (MIBC).

Brigida Anna Maiorano, Joep de Jong, James A. Proudfoot, Giuseppe Basile, Antonio Cigliola, Valentina Tateo, Chiara Mercinelli, Elai Davicioni, Marco Moschini, Michela Ravasi, Giorgio Brembilla, Maurizio Colecchia, Francesco De Cobelli, Alberto Briganti, Francesco Montorsi, Andrea Necchi; IRCCS San Raffaele Hospital, Milan, Italy; Erasmus University Medical Center, Rotterdam, Netherlands; Veracyte, Inc., South San Francisco, CA; Urology Unit, IRCCS San Raffaele Milano, Milan, Italy; IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; IRCCS San Raffaele Hospital, Milano, Italy; Oncology Department, IRCCS San Raffaele Hospital, Milan, Italy; Department of Radiology, IRCCS San Raffaele Hospital, Milan, Italy; Department of Pathology and Laboratory Medicine, IRCCS San Raffaele Hospital, Milan, Italy; IRCCS San Raffaele Scientific Institute, Urological Research Institute (URI), Milan, Italy

Background: Standard of care for MIBC is RC with neoadjuvant chemotherapy (NAC), but ~50% of pts are ineligible for NAC and 5y survival for RC alone is ≤50%. SG is an antibody-drug conjugate composed of an anti-trophoblast cell surface antigen 2 (Trop-2) antibody coupled to SN-38 (a topoisomerase-I inhibitor). SURE-01 (NCT05226117) is an ongoing study testing neoadjuvant SG before RC. Preliminary pathological response rates suggested activity (Cigliola et al., ASCO 2024). Here, we report first results on survival and biomarkers. **Methods:** Pts age ≥18 y, ECOG PS 0-1, with histologically confirmed cT2-T4N0M0 MIBC, ineligible/refusing NAC and scheduled for RC, received 4 cycles of SG 7.5 mg/kg intravenously (reduced dose in protocol amendment 1) on days 1 and 8, Q3W, followed by RC. Primary study endpoint was the proportion of ypT0N0. Secondary endpoints included event-free survival (EFS), relapse-free survival (RFS) post-surgery, overall survival (OS), and safety. EFS included relapse/progression, inability/unwillingness to undergo RC in pts with residual disease, and death. Pts refusing RC with evidence of ypT0 response were censored. Decipher Bladder (Veracyte, San Diego, CA) was used on primary TURBT tissue for transcriptome-wide analyses. Signatera was used for ctDNA assessment. **Results:** From 03/22 to 01/25, 37 pts were enrolled and 33 were efficacy-evaluable. Median age was 71y and 16 pts (48.5%) had cT3-4N0 stage. Twelve pts (36.4%) had mixed variant histology. Grade > 3 treatment-related adverse events (TRAE) occurred in 9 pts (27.3%), including one Grade 5 (at 10mg/Kg dose). Nine pts (27.3%) refused RC and were assessed with a reTURBT. The ypT0N0-x rate was 36.4% (12/33, 95%CI: 20.4-54.9%) and ypT < 1N0-x rate was 39.4% (13/33). 8/10 pts with a high-risk disease at RC had ctDNA-negative status post-RC. Median follow-up was 14 (range 10-17) months. For the intention-to-treat (ITT) population, 12m-EFS was 78.8% (95%CI: 66-94%). 12m-Relapse-free survival (RFS) post-RC/reTURBT was 100% in pts with an ypT < 1N0-x response vs 81.2% in pts with an ypT2-4N0 or ypTanyN1-3 response. Transcriptome-wide data for 27 pts revealed 12m-RFS rate of 100% in N = 8 Infiltrated-Luminal (IL), 86% in N = 7 Claudin Low, 83% in N = 6 Basal and 75% in N = 6 Luminal cases (Log-rank, p = 0.24), with consistent associations found for ypT0 response (IL: 71% ypT0 rate). Lower (< median) *TOP1* gene expression (N = 14) was associated with 100% 12m-RFS rate (Log-rank, p = 0.05). Trop-2 gene expression did not associate to neither ypT response (p = 0.69) nor RFS. **Conclusions:** SURE-01 revealed compelling survival outcomes. While survival estimates or transcriptome results were not overtly associated with pathological response (interim endpoint), molecular subtypes and *TOP1* gene expression may be putative biomarkers of SG efficacy. Clinical trial information: NCT05226117. Research Sponsor: None.

Prognostic impact of histological subtypes in non-muscle-invasive UTUC: Propensity matched analysis.

Shiwang Huang, Yunkai Qie, Chong Shen, Hailong Hu; The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Upper tract urothelial carcinoma (UTUC) is a rare malignancy with poor outcomes. While histological subtypes are known to influence bladder cancer prognosis, their impact on non-muscle-invasive UTUC remains underexplored. This study evaluates the effect of histological subtypes on survival outcomes after radical nephroureterectomy (RNU). **Methods:** This retrospective multicenter study included 399 patients with non-muscle-invasive UTUC who underwent RNU between August 2019 and April 2024. Patients were stratified into pure UTUC (pUTUC) and histological subtype UTUC (hsUTUC) groups. Propensity score matching (PSM) in a 1:2 ratio balanced baseline characteristics. Cancer-specific survival (CSS) was the primary endpoint; recurrence-free survival (RFS) and intravesical recurrence-free survival (IVRFS) were secondary endpoints. Kaplan-Meier curves and Cox regression models were applied for statistical analysis. **Results:** Among 399 patients (median age 69 years; interquartile range [IQR], 63–75), 57 (14%) had hsUTUC. After PSM (166 patients), Kaplan-Meier analysis showed comparable CSS between hsUTUC and pUTUC groups before and after matching ($p > 0.05$). However, hsUTUC patients exhibited significantly worse RFS and IVRFS. Multivariable Cox regression revealed hsUTUC was independently associated with worse RFS (hazard ratio [HR] 2.38, 95% confidence interval [CI] 1.29–4.36; $p = 0.005$) and IVRFS (HR 2.06, 95% CI 1.04–4.10; $p = 0.039$), but not CSS (HR 1.84, 95% CI 0.60–5.61; $p = 0.283$). **Conclusions:** Histological subtypes in non-muscle-invasive UTUC significantly increase recurrence risk but do not affect CSS. These findings highlight the need for tailored surveillance and more aggressive management strategies in hsUTUC patients. Research Sponsor: None.

The association between histological subtypes and survival outcomes.

	Cancer-specific survival		Recurrence-free survival		Intravesical recurrence-free survival	
hsUTUC vs. pUTUC	**HR (95% CI)**	***p value***	**HR (95% CI)**	***p value***	**HR (95% CI)**	***p value***
Unadjusted	1.76 (0.61-5.12)	0.297	2.30 (1.28-4.13)	0.005	1.94 (0.99-3.79)	0.053
Adjusted	1.84 (0.60-5.61)	0.283	2.38 (1.29-4.36)	0.005	2.06 (1.04-4.10)	0.039

Model was adjusted for Tumor T stage (Ta/Tis/T1), lymph node status, lymphovascular invasion, concurrent CIS, concurrent bladder cancer, and hydronephrosis.

Inferring FGFR status from H&E images using digital pathology to identify patients for early-stage bladder cancer targeted therapies.

Albert Juan Ramon, Fatemeh Koochaki, Chaitanya Parmar, Patricia Raciti, Neil Beeharry, Christopher Medberry, Cheng Zhang, David Weingeist, Nicole L. Stone, Spyros Triantos, Joel Greshock, Kristopher Standish; J&J Innovative Medicine, San Diego, CA; Johnson & Johson Innovative Medicine, San Francisco, CA; Johnson & Johnson Innovative Medicine, Spring House, PA; J&J Innovative Medicine, Spring House, PA; Johnson & Johnson Innovative Medicine, New Brunswick, NJ; Johnson & Johnson Innovative Medicine, San Diego, CA; Johnson & Johnson Innovative Medicine, San Francisco, CA; Johnson and Johnson Innovative Medicine, Spring House, PA; Janssen Research & Development, Spring House, PA; Johnson & Johnson, Spring House, PA

Background: The identification of susceptible FGFR (Fibroblast Growth Factor Receptor) alterations may be critical in guiding treatment decisions for patients with bladder cancer. Current nucleic acid-based tests used to detect FGFR+ patients have limitations, including a slow turnaround time and high nucleic acid input requirement, especially in NMIBC, where tissue is often scarce. This study aims toevaluate the performance of an AI-based digital pathology algorithm, MIA:BLC-FGFR, adapted to investigate FGFR alterations in NMIBC patients from routine hematoxylin and eosin (H&E) stained whole slide images (WSIs). This approach may provide a rapid, low-cost, and effective alternative to nucleic acid testing. **Methods:** MIA:BLC-FGFR consists of an image quality control preprocessing stage, a Foundation Model (FM) pre-trained on ~55k unlabeled digital WSIs from various sources (multiple scanners, hospital systems, labs, diseases, tissue sites), and a classification module to enable inference of FGFR status from H&E-stained images. The classification module was trained on datasets (n = 3,067 WSIs) that included a mix of WSIs from multiple sources and disease stages (i.e., NMIBC, muscle-invasive and metastatic bladder cancer), and genetic classification provided by nucleic acid-based test. The algorithm was tuned to achieve a balanced specificity and sensitivity by selecting the operating point with highest F1 score (i.e., balanced sensitivity/specificity) in the training data. As part of this study, we then applied this model to WSIs of biopsies from 3 independent testing datasets (n = 578 WSIs) with varied NMIBC disease settings (i.e., high risk (HR) or intermediate risk (IR)) to evaluate the performance at predicting FGFR status, quantified by the Area Under ROC Curve (AUC). **Results:** MIA:BLC-FGFR demonstrated good concordance with nucleic acid testing methods. The results are summarized in the table below: **Conclusions:** The MIA:BLC-FGFR algorithm adapted to NMIBC can infer the presence or absence of select FGFR alterations from routine H&E images. This AI-based approach may offer a rapid, low-cost, and accurate alternative to traditional nucleic acid testing, particularly benefiting NMIBC patients with limited tumor tissue. By integrating into standard pathology workflows and providing results within minutes, the algorithm has the potential to significantly enhance FGFR testing rates and patient care decisions for emerging FGFR-targeted therapies. Research Sponsor: None.

Testing datasets	Independent Dataset 1	Independent Dataset 2	Independent Dataset 3
Disease setting	HR NMIBC	pT1 IR & HR NMIBC	IR NMIBC
Dataset size (FGFR+ %)	245 (29.7%)	163 (41%)	169 (49%)
PPV	53%	64%	80%
NPA	66%	71%	82%
PPA	89%	73%	76%
auROC	85%	80%	86%

Overall survival and biomarker results of NURE-Combo: A phase 2 study of neo-adjuvant nivolumab (NIVO) and nab-paclitaxel (ABX) followed by postsurgical adjuvant NIVO in patients (pts) with muscle-invasive bladder cancer (MIBC).

Chiara Mercinelli, Giuseppe Basile, James A. Proudfoot, Joep de Jong, Antonio Cigliola, Valentina Tateo, Brigida Anna Maiorano, Elai Davicioni, Michela Ravasi, Maurizio Colecchia, Marco Moschini, Giorgio Brembilla, Francesco De Cobelli, Alberto Briganti, Francesco Montorsi, Andrea Necchi; IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; Urology Unit, IRCCS San Raffaele Milano, Milan, Italy; Veracyte, Inc., South San Francisco, CA; Erasmus University Medical Center, Rotterdam, Netherlands; IRCCS San Raffaele Hospital, Milan, Italy; Veracyte, Inc., San Diego, CA; Oncology Department, IRCCS San Raffaele Hospital, Milan, Italy; Department of Pathology and Laboratory Medicine, IRCCS San Raffaele Hospital, Milan, Italy; Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy; Department of Radiology, IRCCS San Raffaele Hospital, Milan, Italy; Unit of Urology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; IRCCS San Raffaele Scientific Institute, Urological Research Institute (URI), Milan, Italy

Background: The first results of NureCombo revealed the combination of NIVO + ABX followed by RC and adjuvant NIVO was active in pts with MIBC (Mercinelli, JCO 2024). We report key secondary endpoints after study completion including adjuvant NIVO for all pts (NCT04876313). **Methods:** Eligible pts who were cisplatin unfit or declined cisplatin-based treatment had previously untreated MIBC (clinical stage T2-T4a, N0-1, M0), Eastern Co-operative Oncology Group performance status ≤ 1, and predominant (> 50%) UC histology. Pts received 4 cycles of NIVO 360 mg Q3W + ABX 125 mg/m2 on Day 1 and 8, Q3W, followed by RC and by 13 administrations of adjuvant NIVO 360 mg Q3W. Transcriptome-wide analyses with Decipher Bladder (Veracyte, San Diego, CA) on primary TURBT tissue samples are presented. Continuous scores were dichotomized by median splits. **Results:** 31 pts were enrolled from 12/2021 to 06/2023, of which 17 (54.8%) had cT3-4 and 14 (45.2%) cT2. N = 2 (6.4%) had cN1 and 15 (48.4%) had a variant histology component. In total, 9 pts (29%) never started the adjuvant NIVO and 15 pts (48.4%) completed it: reason for discontinuation were treatment-related adverse events (TRAE; 5 pts, 16.1%) and relapse (2 pts; 0.6%). Median follow-up was 25 months (IQR: 21-32) and the minimum follow up was 19 months. In total, 7 pts experienced a relapse, 2/7 consisting of an intravesical relapse in those who refused to undergo RC (N = 3). 24-month (24m) event-free survival (EFS) was 73.7% (95%CI 59.6-91.2), corresponding to the 24m relapse-free survival (RFS) post-RC; 24m overall survival (OS) was 89.7% (95%CI 79.3-100; median OS was not reached). There were no additional/late TRAE compared to the initial report. Transcriptome profiles were available for N = 24: Genomic Subtyping Classifier (GSC) stratification revealed ypT0 was highest (50%) in N = 18 Non-luminal (claudin low, basal & infiltrated-luminal) subtypes and lowest (17%) in N = 6 luminal subtype ((p = 0.34). Based on Consensus MIBC classification, none of N = 4 luminal-papillary tumors had a ypT0 response (p = 0.09). Higher Immune190 and higher ESTIMATE-stromal signature trended to better RFS (HR 0.39 & 0.38, respectively). **Conclusions:** Long-term follow-up results of NureCombo revealed sustained efficacy of ABX-NIVO combination therapy followed by adjuvant NIVO in pts with MIBC. Molecular classification of baseline tumors revealed less favorable pathologic response rates for luminal MIBC. Differences in molecular correlates compared to PURE-01 may be related to different checkpoint inhibition (nivo vs pembro) or due to addition of ABX. Clinical trial information: NCT04876313. Research Sponsor: Bristol Myers Squibb.

Five-year median follow-up update of PURE-01: A phase 2 study of neoadjuvant pembrolizumab followed by radical cystectomy in patients with muscle-invasive bladder cancer (MIBC).

Valentina Tateo, Patrizia Giannatempo, Giuseppe Basile, James A. Proudfoot, Brigida Anna Maiorano, Antonio Cigliola, Chiara Mercinelli, Joep de Jong, Elai Davicioni, Marco Moschini, Michela Ravasi, Simone Rota, Giorgio Brembilla, Maurizio Colecchia, Francesco De Cobelli, Alberto Briganti, Francesco Montorsi, Andrea Necchi; IRCCS San Raffaele Hospital, Milan, Italy; Genitourinary Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milano, Italy; Urology Unit, IRCCS San Raffaele Milano, Milan, Italy; Veracyte, Inc., South San Francisco, CA; IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; Erasmus MC Cancer Institute, Rotterdam, Netherlands; Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy; Oncology Department, IRCCS San Raffaele Hospital, Milan, Italy; Genitourinary Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Department of Radiology, IRCCS San Raffaele Hospital, Milan, Italy; Department of Pathology and Laboratory Medicine, IRCCS San Raffaele Hospital, Milan, Italy; Unit of Urology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; IRCCS San Raffaele Scientific Institute, Urological Research Institute (URI), Milan, Italy; Department of Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy

Background: In patients (pts) with MIBC, the PURE-01 study pioneered the use of neoadjuvant immunotherapy by administering 3 courses of pembrolizumab before radical cystectomy (RC). Multiple reports have outlined various results of this trial, but assessment of the very long-term benefit of this strategy was pending and potentially noteworthy. **Methods:** Pts age ≥18 y, ECOG PS 0-1, with histologically confirmed cT2-T4N0M0 MIBC, ineligible/refusing chemotherapy (CT), and scheduled for RC received 4 cycles of pembrolizumab 200 mg on D1 Q3W, followed by RC and standard-of-care management. A total of 155 pts were included in the study. Even-free survival (EFS), relapse-free survival (RFS) in the RC population and overall survival (OS) are reported. Cumulative risk of recurrence (CRR) by competing risk analyses was also reported. Updated results from transcriptome-wide profiling using the Decipher Bladder assay (Veracyte, San Diego, CA) on primary TURBT tissue are presented. **Results:** From 02/17 to 07/20, 155 pts were treated (12.9% females). Remaining clinical and pathological features yet have been reported. Median follow-up was 61.8 months (IQR: 53.6-68.2). In the intention-to-treat (ITT) population, 5y-EFS was 68.3% (95%CI: 61.1-76.4) and 5y-OS was 77.4% (95%CI: 70.6-84.8). Pathological response categories were significantly associated with both RFS ($p < 0.001$) and OS: 5y-OS for ypT0N0 responders was 89.5% vs 90.3% for ypTa/Tis/T1N0 vs 72.2% for ypT2N0 vs 58.8% for ypT3-4N0 vs 41.9% for ypTanyN+ ($p < 0.001$). Out of 31 total relapses, three were very late relapses > 5y post-RC, of which all were visceral relapses including isolated brain metastases in one case. The 5y-CRR was 19% (95%CI: 13-26). 7/8 pts who refused to undergo RC and received a reTURBT are alive and disease-free. Transcriptome-wide profiles were available for 102 pts. Stratification by Genomic Subtyping Classifier (GSC) allowed significant separation of RFS curves: Claudin Low subtype (N = 14) confirmed to portend the highest 5y-RFS (Log-rank Claudin-Low vs others vs NE-like p = 0.02), with 5y-OS for Claudin Low subtype being 93% (Log-rank Claudin-Low vs others vs NE-like p = 0.29). Higher immune infiltration scores quantified by Immune190 signature were associated with improved OS (HR (95% CI) per 0.1 increase = 0.60 (0.42-0.87); p = 0.006) Biologic evaluation among N = 604 MIBC GRID patients revealed highest Immune190 scores for Claudin Low subtype ($p < 0.001$). **Conclusions:** After > 5y median follow-up, PURE-01 study revealed a sustained response and survival in pts with MIBC. Important updates are the validation of pathological response as a surrogate of OS in post-IO setting, the validation of molecular subtypes in association with RFS (and possibly OS) benefit, and the need to prolong follow-up at long term due to few pts with delayed recurrences. Clinical trial information: NCT02736266. Research Sponsor: Merck Inc.

A phase II prospective, open-label, multi-center, single-arm study of sasanlimab plus sacituzumab govitecan in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) pts: SSANTROP (APRO07-2022).

Joaquim Bellmunt, Alejo Rodríguez-Vida, Imanol Martinez, María José Méndez-Vidal, Carlos Gonzalez, Carlos Alvarez-Fernandez, Nuria Sala González, Oscar Buisan, Maria Jose Miranda Pallares, Pablo Gajate, Ovidio Fernández, Julio Jose Lambea- Sorrosal, José García Sánchez, Daniel Castellano, Elena Sevillano, Martín Lázaro, Federico Jose Vazquez Mazon, Pablo Maroto-Rey, Enrique Gallardo, Oscar Rodriguez Faba; Bladder Cancer Center, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA; Hospital del Mar, IMIM Research Institute, Barcelona, Spain; University Hospital Fundación Jiménez Diaz, Madrid, Spain; Hospital Reina Sofía, Cordoba, Spain; Complejo Hospitalario Regional Virgen Macarena, Sevilla, Spain; Hospital Universitario Central de Asturias, Oviedo, Spain; Catalan Institute of Oncology Girona, Girona, Spain; Hospital Germans Trias i Pujol, Urology Department, Barcelona, Spain; Hospital Sant Joan de Reus, Tarragona, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Complexo Hospitalario Universitario de Ourense, Ourense, Spain; Hospital Clinics Lozano Blesa, Zaragoza, Spain; Hospital Arnau Vilanova Valencia, Valencia, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; HM CIOCC MADRID (Centro Integral Oncológico Clara Campal), Laboratorio de Innovación en Oncología, Instituto de Investigación Sanitaria HM Hospitales, Madrid, Spain; Hospital Álvaro Cunqueiro, Vigo, Spain; Elche General University Hospital, Elche, Alicante, Spain; Department of Medical Oncology, Hospital Sant Pau, Barcelona, Spain; Hospital Universitari Parc Taulí, Sabadell, Spain; Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain

Background: Radical cystectomy (RC)is the standard treatment forBCG unresponsive high-risk (HR) NMIBC patients (pts). Pembrolizumab (Pem) was approved by the FDA based on Keynote-057 (41% complete response rate (CRR)) and offers a non-surgical option for pts who decline or are ineligible for RC. Nadofaregene firadenovec and Nogapendekin alfa inbakicept have been recently approved in this setting. Sacituzumab govitecan (SG) demonstrated encouraging efficacy and safety in metastatic urothelial cancer (mUC) in the TROPHY-U-01 trial. Combining ADCs with immunotherapy showed promising results in mUC. We hypothesized if the combination of sasanlimab (Sa), a subcutaneous (SC) anti-PD1 agent, and SG would improve the CRR of Pem in BCG-unresponsive NMIBC pts who refuse or are ineligible for RC. **Methods:** SSANTROP is a phase II study conducted across 18 sites in Spain to assess the CRR at 3 months (mo) of the combination of Sa (5 cy of Sa 300 mg SC on day 1 every 28 days) plus SG (7 cy of SG 10 mg/kg IV on days 1 and every 21 days) in BCG unresponsive HR NMIBC. Pts achieving CR at 3 mo received maintenance therapy: Sa 300 mg SC every 28-day for up to 2 years. Primary endpoint was CRR at 3 mo with plan for percentage of response assessment maintained at 12 and 15 mo. Key eligibility criteria: ECOG PS 0-1, histologically confirmed BCG-unresponsive HR NMIBC, refusal or ineligibility for RC, urothelial carcinoma histology, and no prior anti-PD1/L1 or anti-CTLA-4 therapy. The sample size of 116 pts was calculated to demonstrate a 53% CRR for the combination, based on a Pem historical control of 41% (one-sided alpha 0.05, power 82%). Design was modified to finally include 40 pts based on a change in the treatment landscape of UC. **Results:** As of January 21, 2025, 59 pts were screened, and 41 initiated treatment and were included in the safety analysis. Among them, 32 (78%) male, median age of 70.6 years (SD 7.8). Types of BCG-unresponsive disease included: persistent/recurrent CIS alone or with recurrent HG Ta/T1 within 12 mo post-BCG (22 pts, 53.7%), recurrent HG Ta/T1 within 6 mo post-BCG (16 pts, 39%), and T1 HG disease at first evaluation post-induction BCG (3 pts, 7.3%). The most common adverse events (AEs) were diarrhea (58.5%), asthenia/fatigue (58.5%), alopecia (41.5%), neutropenia (36.6%), anemia (24.4%) and stomatitis (22%). Most common grade $\geq$ 3 AEs included neutropenia (9 pts, 22%), febrile neutropenia (5 pts, 12.2%). G-CSF prophylaxis was implemented as of 09/2024. As of 12/2024 and based on 25 evaluable pts, CRR at 3 mo was 68% (17/25). **Conclusions:** This trial is the first to evaluate the combination of Sa and SG in BCG-unresponsive HR-NMIBC. With preliminary 3 mo CRR of 68%, the safety analysis identified no unexpected concerns, with severe AEs mainly involving neutropenia and febrile neutropenia. No treatment related toxic deaths occurred. Clinical trial information: 2022-002998-28. Research Sponsor: Pfizer, Gilead.

Impact of tumor burden or focality in recurrent low-grade intermediate-risk non-muscle invasive bladder cancer on response to treatment with UGN-102: A sub-study of the phase 3 ENVISION trial.

John Sfakianos, Dimitar Shishkov, Nikola V. Mihaylov, Alexandre Khuskivadze, Pencho Genov, Vasyl Terzi, Max Kates, Willliam C. Huang, Michael J. Louie, Sunil Raju, Brent Burger, Andrew Meads, Sandip M. Prasad, The ENVISION Study Group; Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY; Department of Urology, University Multiprofile Hospital for Active Treatment, Plovdiv, Bulgaria; Urology Department, Georgia Israel Joint Clinic Gidmedi, Tbilisi, Georgia; Urology Department, University Multiprofile Hospital for Active Treatment Kanev, Ruse, Bulgaria; Multiprofile Hospital for Active Treatment Varna Military Medical Academy, Varna, Bulgaria; The Johns Hopkins University School of Medicine, Baltimore, MD; NYU Langone Urology Associates, New York, NY; UroGen Pharma, Princeton, NJ; Morristown Medical Center/Atlantic Health System and Garden State Urology, Morristown, NJ

Background: In the ENVISION pivotal phase 3 study (NCT05243550) patients with low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC) were treated with UGN-102, a reverse thermal hydrogel containing mitomycin. Primary efficacy and safety results were previously reported. Complete response rate (CRR) at 3 months was 79.6%, with an 82.3% probability of remaining in response at 12 months by Kaplan–Meier estimate. Here, we present a post-hoc analysis evaluating if multifocality and tumor size influenced response rate and durability. **Methods:** In the single-arm ENVISION study, 240 patients with LG-IR-NMIBC received 6 weekly intravesical instillations of UGN-102; 3 months after the first dose, patients were examined for the presence of bladder cancer using cystoscopy, urine cytology testing, and for-cause biopsy. Patients achieving complete response (CR; no detectable disease) underwent follow-up with surveillance cystoscopy. In pre-specified subgroups, comparisons of patients with tumor burden (calculated as total length of all tumors) $\leq$3cm vs $>$ 3 cm and single vs multiple tumors were performed for CRR at 3 months and hazard ratios (HRs) of duration of response (DoR) at 12 months after achieving CR. For the comparison of CRR, p values were calculated using Fisher's Exact Test. HRs of DoR were calculated using a Cox proportional hazards model, and p values calculated using a log-rank test. Comparisons were not powered to identify a difference and p values were unadjusted for multiple comparisons. **Results:** CRR at 3 months was 82.8% vs 73.2% for patients with tumor burden $\leq$3 cm and $>$ 3 cm, respectively. Of patients with CR at 3 months with tumor burden $\leq$3 cm and $>$ 3 cm, 15.4% vs 20%, respectively, experienced either recurrence of LG disease, progression (either stage or grade), or death by 15 months. In patients with multiple vs single tumors, 3-month CR was 79.3% vs 82.9%; recurrence rates were 18.5% vs 11.8%. DoR HRs were not statistically significant for any comparison made (Table). **Conclusions:** The CRR and DoR were favorable in all subgroups and no significant differences were observed. Study limitations were the small sample size of comparator groups, single arm design, and post-hoc nature of the analysis. UGN-102 may represent a valuable treatment option for many patients with LG-IR-NMIBC. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma.

	CR at 3 months	CRR ratio (95% CI)/p value	Recurrence within 15 months[a]	DoR HR (95% CI)/p value
Tumor burden				
≤3 cm	149/180 (82.8%)	1.13 (0.93, 1.38)	23/149 (15.4%)	0.777 (0.317, 1.909)
>3 cm	30/41 (73.2%)	p=0.1854[b]	6/30 (20.0%)	p=0.5816[b]
Tumor count				
Multiple	157/198 (79.3%)	0.96 (0.82, 1.12)	29/157 (18.5%)	1.644 (0.578, 4.677)
Single	34/41 (82.9%)	p=0.6740[b]	4/34 (11.8%)	p=0.3459[b]

[a]3-month CR patients only.
[b]Nominal.
CI, confidence interval.

Duration of response (DoR) following treatment with UGN-102 in patients with recurrent, low-grade, intermediate-risk, non-muscle invasive, bladder cancer: 18-month DoR data from the phase 3 ENVISION trial.

Sandip M. Prasad, Nikola V Mihaylov, Alexandre Khuskivadze, Pencho Genov, Vasyl Terzi, Max Kates, William C. Huang, Michael J. Louie, Sunil Raju, Brent Burger, Andrew Meads, Dimitar Shishkov, on behalf of The ENVISION Study Group; Morristown Medical Center/Atlantic Health System and Garden State Urology, Morristown, NJ; Department of Urology, University Multiprofile Hospital for Active Treatment, Plovdiv, Bulgaria; Urology Department, Georgia Israel Joint Clinic Gidmedi, Tbilisi, Georgia; Urology Department, University Multiprofile Hospital for Active Treatment Kanev, Ruse, Bulgaria; Multiprofile Hospital for Active Treatment Varna Military Medical Academy, Varna, Bulgaria; The Johns Hopkins University School of Medicine, Baltimore, MD; New York University Langone Medical Center, New York, NY; UroGen Pharma, Princeton, NJ

Background: Low-grade, intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC) is a recurrent cancer inadequately controlled by the current standard of care: transurethral resection of bladder tumor (TURBT). ENVISION (NCT05243550), is an ongoing prospective, phase 3, multinational, single-arm trial, evaluating UGN-102 in patients with a history of LG-NMIBC requiring TURBT. Primary efficacy and safety results have been published previously,[1] here we report long term efficacy data with 18 months follow-up after complete response (CR) to UGN-102 at 3 months. **Methods:** Patients received6 weekly intravesical instillations of UGN-102, a reverse thermal hydrogel containing mitomycin (75 mg). 3 months after the first instillation of UGN-102, patients underwent cystoscopy, urine cytology testing, and for-cause biopsy, to determine the presence or absence of bladder cancer. Secondary endpoints included duration of response (DoR), defined as the time from CR at 3 months to the earliest date of disease recurrence, progression, or death from any cause, whichever occurred first. DoR data was calculated for all patients with a minimum follow-up of 18 months after 3-month CR was calculated using Kaplan–Meier (KM) method. **Results:** 240 patients with recurrent LG-IR-NMIBC were enrolled and received at least one dose of UGN-102; 95% (228) received all 6 doses. Patients were mainly white (98%), male (61%) and aged over 65 years old (68%). CR at 3 months was achieved by 191 patients (79.6%; 95% CI: 73.9–84.5). For these patients, the probability of remaining in response 18-months after CR was 80.6% (95% CI 74.0-85.7; KM estimate). Of those who experienced recurrence post CR, most experienced LG disease (17.3%). **Conclusions:** In the ENVISION study treatment with UGN-102 in patients with recurrent LG-IR-NMIBC resulted in a high and clinically meaningful CR rate. Patients who achieved an initial CR at 3 months had a high probability of remaining disease-free 18 months later. This data confirms that UGN-102 represents a valuable treatment option for patients with LG-IR-NMIBC. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma. Pharmaceutical/Biotech Company.

	UGN-102
CR at 3 months (95% CI)	**191/240, 79.6% (73.9–84.5)**
Follow-up time (months) for DoR, Median, months (95% CI)*	**18.73 (18.23–20.27)**
DoR by Kaplan–Meier estimate at 18 months post CR	**80.6% (95% CI 74.0–85.7)**
Patients with events at 18 months post CR	**39/191 (20.4%)**
LG disease	**33/191 (17.3%)**
Progression**	**4/191 (2.1%)**
Death	**2/191 (1.0%)**

*3-month CR patients only, estimated using reverse KM;
**Includes progression to high grade (HG) disease, T1 (Tumor Invades Lamina Propria), and Cis (Carcinoma in situ).
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Determinants in trimodality therapy for bladder cancer: Overcoming chemoradiotherapy resistance via ferroptosis.

Takuya Tsujino, Shogo Yamazaki, Kazuki Nishimura, Kazumasa Komura, Haruhito Azuma; Osaka Medical and Pharmaceutical University, Takatsuki, Japan

Background: Expanding bladder preservation therapy can improve quality of life in patients with bladder cancer. This study aims to identify genetic determinants associated with trimodality therapy (TMT) for bladder preservation in bladder cancer (BC) patients and develop novel strategies to overcome chemoradiotherapy (CRT) resistance. **Methods:** Multi-omics analysis integrating RNA sequencing and whole exome sequencing (WES) was performed on clinical BC samples from 200 patients who underwent TMT in the OMPU-NCC dataset. The genomic profile of CRT-resistant BC cell lines was also analyzed. Ferroptosis signature scores were calculated using genes curated from the FerrDbV2 database. **Results:** WES revealed frequent alterations in DNA damage response (DDR) genes (Fig. 1A). Kaplan-Meier analysis showed significantly improved progression-free survival (PFS; HR 0.5840, 95% CI 0.3891-0.8765, P = 0.0157) and overall survival (OS; HR 0.5384, 95% CI 0.3331-0.8700, P = 0.0296) in patients with DDR alterations (Fig. 1B). Transcriptomic analysis identified distinct expression profiles between responders and progressors post-TMT. Gene Ontology analysis showed downregulation of immune response and lipid metabolism pathways in progressors (Fig. 2A). Analysis of the ferroptosis signature, which links these pathways, indicated that a high ferroptosis-suppressor signature score was correlated with worse survival outcomes (PFS: HR 2.713, 95% CI 1.818-4.047, $P < 0.0001$; OS: HR 2.311, 95% CI 1.502-3.557, P = 0.0001), in contrast to the driver signature (Fig. 2B). RNA-sequencing of cell lines revealed significant differences in ferroptosis signature between parental and CRT-resistant strains (Fig. 2C). The combination of the ferroptosis inducer and irradiation overcame resistance in the T24R cell line, which is enriched with ferroptosis-suppressor genes. **Conclusions:** Key survival determinants post-CRT were highlighted, positioning ferroptosis as a target for overcoming resistance (Fig. 2D). Combining ferroptosis inducers with irradiation could offer a new therapeutic avenue for expanding bladder preservation. Research Sponsor: Japan Society for the Promotion of Science; No. 23K14606; Osaka Medical and Pharmaceutical University Research Promotion Project Grant.

Survival outcome after TMT according to DDR alteration and ferroptosis signature score.

Status	Number of patients	PFS after TMT (median, months)	HR (95% CI)	OS after TMT (median, months)	HR (95% CI)
DDR intact	49	25	ref	48	ref
DDR alteration	151	61	0.584 (0.389 to 0.877)	NR	0.538 (0.333 to 0.870)
Ferroptosis signature low	102	NR	ref	NR	ref
Ferroptosis signature high	98	16	2.713 (1.818 to 4.047)	27	2.311 (1.502 to 3.557)

PFS = progression free survival, TMT = trimodality therapy, HR = hazard ratio, CI = confidence interval, OS = overall survival, DDR = DNA damage response, NR = not reached.

Survival outcomes of whole pelvic vs. bladder-only radiation in muscle-invasive bladder cancer: A nationwide large-scale study.

Mohammad Arfat Ganiyani, Atulya Aman Khosla, Manas Pustake, Rajiv Doddamani, Nouman Aziz, Zouina Sarfraz, Adeel Kaiser, Marcio Fagundes, Rohan Garje; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Corewell Health William Beaumont University Hospital, Royal Oak, MI; Texas Tech University Health Sciences Center, El Paso, TX; Glenwood Regional Medical Center, West Monroe, LA; Wyckoff Heights Medical Center, Brooklyn, NY

Background: Muscle-invasive bladder cancer (MIBC) is an aggressive malignancy traditionally managed with definitive surgery combined with systemic therapy. However, bladder-preservation approaches, including concurrent chemoradiation, offer alternatives for patients unfit for surgery. Within bladder-preservation, the choice between whole pelvic radiation (WP-RT) and bladder-only radiation (BO-RT) remains debated. WP-RT may address microscopic lymphatic disease, while BO-RT minimizes radiation toxicity. This study aims to compare survival outcomes between WP-RT and BO-RT utilizing the National Cancer Database. **Methods:** This retrospective study included patients with MIBC (T1-4a, N0-2, M0) from 2004-2020. It focused on individuals who received radiation therapy and underwent the maximum feasible local resection without definitive surgery. Kaplan-Meier analysis and a multivariate Cox proportional hazards model were used to evaluate survival outcomes based on the radiation field in patients with MIBC. **Results:** This study analyzed 18,659 patients with MIBC, including 18,092 who received BO-RT and 567 who underwent WP-RT. Among these, 71.76% received systemic therapy. Notably, the use of systemic therapy was more common in the WP-RT group (89.24%) compared to the BO-RT group (71.21%). The median overall survival was 23.33 months for patients treated with BO-RT compared to 38.7 months (Log rank P<0.001) for those who underwent WP-RT. In our adjusted analysis, patients treated with WP-RT had a 35% lower risk of death (HR: 0.65, 95% CI: 0.55–0.76, P < 0.001) compared to those receiving BO-RT, irrespective of receiving systemic therapy. Additionally, the use of concurrent chemoradiation was associated with a 50% reduction in the risk of death (HR: 0.50, 95% CI: 0.48–0.51, P < 0.001). **Conclusions:** This study found that in patients with MIBC, WP-RT was independently associated with better overall survival compared to BO-RT. These findings highlight the survival benefits of targeting microscopic lymphatic disease with WP-RT, while weighing the risks of associated toxicity. Additionally, Concurrent systemic therapy significantly reduced the risk of death, emphasizing its vital role in improving survival outcomes. Research Sponsor: None.

Cox proportional model in patients with muscle invasive bladder cancer.

Variable	HR (95% CI)	P-value
Charlson Score		
0		
>=1	1.24 (1.20–1.29)	< 0.001
Radiation Field		
Bladder Only		
Pelvic + Bladder	0.65 (0.55–0.76)	< 0.001
Histology		
Urothelial		
Non-Urothelial	1.23 (1.16–1.30)	< 0.001
Concurrent Chemoradiation		
No		
Yes	0.50 (0.48–0.51)	< 0.001

Assessing real-world recurrence in high-risk (HR) non-muscle-invasive bladder cancer (NMIBC) treated with bacillus Calmette-Guérin (BCG) in the United States through a recurrence algorithm: A SEER-Medicare study.

Yair Lotan, Rituparna Bhattacharya, Honghao Fang, Sandy S. Chang, Yizhen Lai, Shujing Zhang, Jiayang Li, Pangsibo Shen, Wei Gao, Yan Song, Hema Dave, Haojie Li; Department of Urology, UT Southwestern Medical Center, Dallas, TX; Merck & Co., Inc., Rahway, NJ; Analysis Group, Inc., Montreal, QC, Canada; Analysis Group, Inc., Boston, MA

Background: Assessing bladder recurrences in real-world setting can be challenging due to the lack of readily available data on recurrence in large real-world databases (e.g., SEER-Medicare), which limits the ability to evaluate the long-term real-world outcomes. To address this, this study developed an algorithm using linked SEER-Medicare data (2007–2020) to identify and classify recurrence events. **Methods:** A retrospective cohort study in patients with HR-NMIBC treated with BCG was conducted, with BCG initiation as the index date. A recurrence algorithm was developed to identify and classify recurrence events including NMIBC recurrence, muscle-invasive bladder cancer (MIBC) progression, and distant metastasis (DM). NMIBC recurrence and MIBC progression were identified based on repeat TURBT procedures occurring ≥30 days after the last BCG treatment, supplemented by cancer diagnoses in the urethra or upper tract. Subsequent treatments were used to further classify them as NMIBC recurrence (intravesical BCG after a ≥6-month gap from the last BCG, or intravesical chemotherapy) and MIBC progression (systemic therapy, radiotherapy, or cystectomy). DM was identified by urothelial cancer diagnoses outside the urinary bladder, urethra, or upper tract. Cumulative incidence rates from the index date for each recurrence type were calculated accounting for competing events, such as death and more severe types of recurrences (e.g., MIBC or DM for NMIBC recurrence). **Results:** A total of 5,490 patients (median follow-up: 2.9 years) were included. Median age at index diagnosis was 76.5 years. NMIBC recurrence was the most common type of recurrences, followed by MIBC progression and DM. The cumulative incidence rates were 15.9% for NMIBC recurrence, 4.1% for MIBC progression, and 3.7% for DM at 1 year, reaching 33.6%, 15.9%, and 16.7% at 10 years, respectively (Table). **Conclusions:** Using linked SEER-Medicare data, an algorithm was developed to identify and classify disease recurrences, facilitating long-term outcomes analyses in a large, real-world cohort. Notably, most recurrences occurred within the first 5 years from BCG initiation, after which rates plateaued. These findings underscore the importance of routine imaging for early detection and timely intervention and the need for better treatments to reduce recurrence and progression burden in this population. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Cumulative incidence rates by type of recurrences (N = 5,490)[1].

Recurrence type	Number of events during the follow-up period	1 year	3 years	5 years	7 years	10 years
NMIBC recurrence	1528	15.9%	28.7%	31.6%	32.6%	33.6%
MIBC progression	552	4.1%	9.3%	12.1%	14.0%	15.9%
DM	528	3.7%	8.1%	11.5%	13.5%	16.7%

[1]Patients were censored at the end of continuous eligibility or the end of data availability, whichever occurred earlier.

Correlation of circulating tumor DNA (ctDNA) dynamics with clinical response in muscle-invasive bladder cancer (MIBC) patients (pts) undergoing trimodality therapy (TMT).

Ilana Bensussen Epstein, Adetolani Odogiyon, Stephanie A. Berg, Yukako S. Otani, Charlene Mantia, Isabella R. Pompa, Matthew Mossanen, Joshua J. Wan, Anurag Saraf, Arvind Ravi, Filipe LF Carvalho, Daniel Aaron Roberts, Luke Peng, Bradley Alexander McGregor, Joaquim Bellmunt, Sophia C. Kamran, Jacob E. Berchuck, Jason A. Efstathiou, David T. Miyamoto, Kent William Mouw; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA

Background: TMT is a curative treatment option for pts with MIBC. Plasma circulating tumor DNA (ctDNA) is associated with treatment response and clinical outcomes following cystectomy for MIBC, but the association of plasma ctDNA with treatment response and clinical outcomes in pts treated with TMT is poorly understood. We hypothesize that ctDNA dynamics are correlated with clinical outcomes in pts with MIBC treated with TMT. **Methods:** Pts with MIBC who received TMT at Dana-Farber/Brigham and Women's Cancer Center or Massachusetts General Hospital, consented to a research protocol, and underwent ctDNA evaluation with the commercially available Signatera assay were included in the analysis. Individual chart review was performed to collect demographic and clinical data. **Results:** A total of 67 pts had at least one ctDNA evaluation and were included in this analysis. Cohort characteristics are summarized in Table 1. Forty-eight pts had at least one ctDNA evaluation prior to TMT, and 17 (35%) were ctDNA(+). Of the pts who were ctDNA(+) prior to TMT, 12 had at least one post-TMT ctDNA evaluation and 7 of 12 (58%) converted to ctDNA(-). Thirty-one pts were ctDNA(-) prior to TMT: 24 (77%) have had ≥1 post-TMT ctDNA evaluation and all 24 remained ctDNA(-) at the first post-TMT evaluation (median 8 weeks after TMT completion). Of the 55 pts with ≥1 post-TMT ctDNA result, 46 (84%) have remained ctDNA(-) during subsequent follow-up and do not have clinical evidence of recurrence (median number of ctDNA evaluation, 2; median follow up, 44 weeks). Nine pts had a ctDNA(+) result in the post-TMT setting: 5 were also ctDNA(+) prior to TMT, 2 did not have a pre-TMT ctDNA assessment but were ctDNA(+) at first-post TMT assessment, and 2 were ctDNA(-) before and initially after TMT but subsequently converted to ctDNA(+). Of these 9 ctDNA(+) cases, 6 pts (67%) have developed clinical evidence of metastatic disease to date with a median lead time of 5.3 weeks (range, 0-27 weeks) between first ctDNA(+) assessment and clinical evidence of metastatic disease. Overall, the sensitivity of plasma ctDNA testing in the post-TMT setting was 100% and the specificity was 94%. **Conclusions:** Most pts with MIBC treated with TMT in this cohort were ctDNA(-) following TMT and did not develop evidence of recurrent invasive or metastatic disease. Pts with ctDNA(+) status in the post-TMT setting frequently developed clinical evidence of metastatic disease. Larger cohorts with longer follow-up will be required to determine whether ctDNA status may be useful in guiding clinical decisions in MIBC pts undergoing TMT. Research Sponsor: None.

No. of Pts	67
Median Age (Yrs)	75
M:F	59:8
T3-4 (%)	16 (24%)
≥N1 (%)	3 (4%)
Presence of variant histology (%)	13 (19%)
Received neoadjuvant chemotherapy (%)	12 (18%)
Received concurrent chemotherapy (%)	61 (91%)
Median RT dose (Gy)	55
Median length of follow up (weeks)	39

Pathologic response and safety of neoadjuvant pembrolizumab with or without entinostat in muscle-invasive urothelial cancer (MIUC).

Tracy L. Rose, Pooja Ghatalia, Allison Mary Deal, Marc Bjurlin, Hung-Jui Tan, Young E. Whang, Blaine Y. Brower, Mary Dunn, William Y. Kim, Matthew I. Milowsky; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Fox Chase Cancer Center, Philadelphia, PA; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC; The University of North Carolina Center at Chapel Hill, Chapel Hill, NC; Department of Medicine, The University of North Carolina School of Medicine, Chapel Hill, NC

Background: Entinostat (Ent) is a selective histone deacetylase 1/3 inhibitor that potentiates immune checkpoint inhibitor activity in immunocompetent mouse models of urothelial cancer through immune editing of tumor neoantigens resulting in tumor immune microenvironment remodeling and associated changes in immune gene signature expression (J Clin Invest. 2021). Pembrolizumab (P), an immune checkpoint inhibitor, has demonstrated activity as neoadjuvant therapy for muscle-invasive urothelial cancer (MIUC) with the potential for combination treatment with Ent to improve outcomes. **Methods:** LCCC1827 is a window of opportunity trial of P with or without Ent in cisplatin-ineligible patients with T2-4aN0M0 MIUC prior to definitive therapy with radical cystectomy (RC) or trimodality therapy (TMT) with maximal TURBT followed by chemoradiation (NCT03978624). Patients were treated with P 200mg IV on day 1 and day 22 alone (Arm 1) or P 200mg IV on day 1 and 22 in combination with Ent 5mg po on days 1, 8, 15 (Arm 2) followed by definitive treatment within 10 weeks of day 1. The primary endpoint was change in immune gene signature expression in pre- and post-treatment tumors in Arm 2 compared to Arm 1. Here, we report clinical and secondary endpoints of pathologic response rate (pRR, < pT2N0) and pathologic complete response (pCR, pT0N0) for patients with RC, clinical complete response rate (cT0) at repeat TURBT for patients with TMT, and safety. **Results:** 20 patients (10 P; 10 P-Ent) were enrolled between 09/2020 and 10/2023 (85% male; median age 76 years; 25% black; 75% clinical T2) with all patients completing protocol-defined neoadjuvant therapy. 19 patients underwent definitive therapy (1 refused; 14 RC and 5 TMT). For RC, pRR was 43% and pCR was 29% in each arm. For TMT, cT0 was 100% in Arm 1 (n = 2) and 66% in Arm 2 (n = 3). Most common treatment-related AEs were diarrhea (20% in both arms), nausea (10% Arm 1, 30% Arm 2), and fatigue (10% Arm 1, 20% Arm 2). Grade 3 or higher treatment-related adverse events occurred in two patients (10%) (myalgias and back pain in one patient on Arm 1, hyponatremia in one patient on Arm 2). No patients had RC or TMT delayed due to treatment-related adverse events. All patients completed RC within 10 weeks of study initiation, except for 1 patient who delayed cystectomy for logistical reasons. One patient died after RC due to complications unrelated to study treatment. **Conclusions:** Neoadjuvant pembrolizumab with or without entinostat is active in MIUC with an acceptable safety profile. Analysis of the primary endpoint and other translational endpoints is ongoing. Clinical trial information: NCT03978624. Research Sponsor: Merck.

Subsequent treatments and outcomes in bacillus Calmette-Guerin–unresponsive patients with high-risk non-muscle invasive bladder cancer with carcinoma in situ: A real-world data analysis.

Ariel B. Bourla, Ran Sun, Shalaka Hampras, Bolan Linghu, Jose Zamalloa, Emily Scherer, Wendy Crist, Sabine D. Brookman-May, Joel Greshock, Jessica Chung, Hussein Sweiti; Johnson & Johnson, New Brunswick, NJ; Johnson & Johnson, Brisbane, CA; Johnson & Johnson, Raritan, NJ; Johnson & Johnson, Boston, MA; Johnson & Johnson, Titusville, NJ; Johnson & Johnson, Spring House, PA

Background: Intravesical (ives) Bacillus Calmette-Guerin (BCG) is the recommended first-line treatment (tx) option for patients (pts) with high-risk (HR) non-muscle-invasive bladder cancer (NMIBC). Despite initial activity, BCG fails in up to 50% of pts. Pts with BCG unresponsive HR NMIBC with Carcinoma in situ (CIS) are at high-risk of disease progression. Limited evidence is available about tx patterns and outcomes of these pts. The objective of this study is to characterize real-world tx patterns and assess corresponding outcomes. **Methods:** This retrospective cohort study utilized comprehensive claims augmented with electronic health records in the US HealthVerity dataset from Oct 2015 to Dec 2022. This analysis included NMIBC pts who received adequate BCG (> = 7 doses) and had a CIS recurrence within 12 months of last BCG dose. Recurrence with CIS is defined as a transurethral resection of bladder tumor (TURBT) followed by a CIS diagnosis (dx) within 30 days. Descriptive analysis to characterize subsequent tx post BCG was performed for pts with at least 1 year of follow up post-recurrence. Time to recurrence or progression (defined as a TURBT followed by a BC dx within 30 days or starting a new line of tx) was used to assess outcomes of subsequent tx using Kaplan-Meier analysis. **Results:** We identified 23,280 pts with NMIBC who were treated with BCG between 2015 and 2022. Overall, 11,116 pts (48%) received > = 7 BCG doses and 1,094 pts recurred with CIS within 12 months of last BCG dose. Among them, 486 pts (44.4%) with BCG unresponsive HR NMIBC with CIS [79% males, median age 66 years (IQR: 60, 75)] received subsequent therapy. Median time from recurrence to tx initiation was 91 days (IQR: 41, 346). The most frequently administered tx was ives chemotherapy (ctx), accounting for 45% of cases (Table 1). Among pts receiving ives ctx (n = 217), 68% experienced recurrence or progression within 12 months with a median time to recurrence or progression of 174 days [139, 196]. **Conclusions:** Although guidelines recommend radical cystectomy for BCG unresponsive HR NMIBC patients with CIS, this RWD analysis revealed that over half of these patients received no further treatment for at least 1 year after their disease recurrence or progression. Among those treated, ives ctx was the most common tx. Therefore, the majority of patients were either undertreated or received ives ctx with only modest outcomes. This highlights the need for novel, more effective bladder-sparing therapies in this pt population. Research Sponsor: None.

Subsequent line of treatment for BCG unresponsive HR NMIBC patients with CIS post BCG.

Subsequent Treatment	N =486 pts
Intravesical ctx	217 (45%)
Radical cystectomy	121 (25%)
Intravesical BCG*	66 (14%)
Interferon alpha + BCG	60 (12%)
Systemic immunotherapy	22 (4%)

*BCG treatment starting > 12 months post the last BCG dose is considered a new line of treatment.

Intravesical disitamab vedotin (RC48) for patients with HER2-expressing high-risk non-muscle-invasive bladder cancer: A dose-escalation phase I trial.

Xu Chen, Ming Huang, Jianmin Fang, Jian Huang, Tianxin Lin; Sun Yat-sen Memorial Hospital, Guangzhou, China; School of Life Science and Technology, Tongji University, Shanghai, China; Department of Urology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

Background: HER2 expression is associated with poor efficacy of Bacillus Calmette-Guérin (BCG) instillation in patients (pts) with high-risk non-muscle-invasive bladder cancer (HR-NMIBC). Developing effective treatment for HER2-expressing HR-NMIBC is of great urgency. Our previous study demonstrated that intravesical disitamab vedotin (DV, RC48, an anti-HER2 antibody-drug conjugate) had promising anti-tumor effects in the orthotopic BCa mouse model (Hong, X. et al., *Advanced Science*, 2023). We aimed to evaluate the safety and efficacy of intravesical DV in pts with HER2-expressing HR-NMIBC. **Methods:** Key eligibility criteria included HR-NMIBC (stage: cTa/T1±CIS, N0, M0) pts who were unsuitable for cystectomy, 18-75 years of age, HER2-expressing (IHC 1/2/3+) , BCG naive or BCG-unresponsive, and conducted transurethral resection of bladder tumor (TURBT) within 3 weeks prior to study treatment. Pts received intravesical DV (60, 120, or 180 mg) following a 3+3 design once weekly for six weeks (induction), followed by optional DV maintenance treatment once monthly until disease recurrence/progression, intolerable toxicity, or completion of nine treatments. The primary objective of this study was to assess the safety and tolerability of DV. The scheduled efficacy assessment included ultrasound and cystoscopic examination every three months. This study was registered with ClinicalTrials.gov, NCT06378242. **Results:** Between August 15, 2023 and December 1, 2024, nine pts were enrolled and completed the induction treatments at designated doses; no dose-limiting toxicities (DLTs) or any≧grade 3 treatment-related adverse events (TRAEs) occurred. The most common TRAEs included urinary tract infection (55.6%, 5/9), pollakiuria (11.1%, 1/9) and hematuria (11.1%, 1/9). All the patients underwent regular efficacy assessments, except for one patient who withdrew from the study in advance. As of December 1, 2024, after a median follow-up of 12.0 months (interquartile range [IQR]: 9.0–12.3), two pts developed recurrent disease, and no disease progression occurred. At 6 months, 8 pts were assessed for efficacy; both recurrence-free survival (RFS) and progression-free survival (PFS) were 100%. At 12 months, 6 pts were efficacy-evaluable; RFS rate was 83.3% (95% CI: 27.3, 97.5) and PFS rate was 100%. **Conclusions:** Intravesical DV was well-tolerated and showed preliminary efficacy in pts with HER2-expressing BCG-naive/unresponsive HR-NMIBC. The maximum tolerated dose was not reached, further dose exploration is ongoing in RC48-C029 study (NCT06378242). Clinical trial information: NCT06378242. Research Sponsor: None.

IL-15RαFc superagonist SHR-1501 with or without bacille Calmette Guerin (BCG) for high-risk non-muscle invasive bladder cancer (NMIBC): A phase 1/2 study.

Yuke Chen, Hailong Hu, Shan Liang, Jianming Guo, Wei Xue, Lianhua Zhang, Haitao Niu, Yu Cao, Xiang Wang, Hang Huang, Hongqian Guo, Zengjun Wang, Lei Li, Danfeng Xu, Xin Xie, Xianfeng Zhou, Jiaqin Lin, Mingming Zhang, Denghui Gao, Zhisong He; Peking University First Hospital, Beijing, China; The Second Hospital of Tianjin Medical University, Tianjin, China; Zhongshan Hospital, Fudan University, Shanghai, China; Shanghai Jiao Tong University School of Medicine Renji Hospital, Shanghai, China; The Affiliated Hospital of Qingdao University, Qingdao, China; Shanghai First People's Hospital, Shanghai, China; The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Institute of Urology, Nanjing, China; The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: BCG is the standard therapy after transurethral resection of bladder tumor for high-risk NMIBC. IL-15 agonists can enhance the immune response induced by BCG via stimulating the proliferation and activation of natural killer cells and CD8+ cytotoxic T cells, without inducing regulatory T cells. SHR-1501 is an IL-15 agonist fusion protein, composed of a humanized antibody Fc region fused with IL-15 and IL-15Rα sushi domain. In this phase 1/2 study, we assessed the safety, tolerability, and efficacy of SHR-1501 in patients (pts) with high-risk NMIBC. **Methods:** The study comprised dose-escalation phase 1a and 1b parts of SHR-1501 alone or in combination with BCG in pts with high-risk NMIBC, followed by a phase 2 part of SHR-1501 plus BCG in multiple cohorts, including pts with BCG-naive NMIBC (cohort A), BCG-unresponsive NMIBC carcinoma in situ (CIS; cohort B), and BCG-unresponsive high-grade Ta/T1 NMIBC without CIS (cohort C). All pts received intravesical study treatment weekly for 6 weeks during induction period. During maintenance period, instillations occurred weekly for the first 3 weeks at 3, 6, 12, 18, and 24 months after the initial induction instillation. Primary endpoints were dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended phase 2 dose in phase 1a and 1b parts; and was complete response (CR) rate for cohort B and 12-mo disease-free survival (DFS) rate for cohorts A and C in phase 2 part. **Results:** As of Sep 7, 2024, 84 pts were enrolled (n = 8 in phase 1a; n = 6 in phase 1b; n = 29, 17, and 24 in cohorts A, B, and C in phase 2). In phase 1a part of SHR-1501 alone (200, 400, and 600 μg) and phase 1b part of SHR-1501 (600 μg) plus BCG (120 mg), no DLTs were observed, and MTD was not reached. Thus, 600 μg of SHR-1501 plus 120 mg of BCG was used in phase 2 part. Treatment-related adverse events (TRAEs) occurred in 4 (50.0%) of 8 pts with SHR-1501 and 53 (69.7%) of 76 pts with SHR-1501 + BCG. Grade 3 TRAEs were reported in 1 (12.5%) pt with SHR-1501 (urinary tract infection) and 7 (9.2%) pts with SHR-1501 + BCG (urinary tract infection and hypertension occurred in $>$ 1 pt). No grade 4 or 5 TRAEs were reported. No serious TRAEs occurred. Of the efficacy evaluable pts in cohort B, the CR rate at 3 or 6 months was 90.9% (10/11). In cohorts A and C, the 12-month DFS rate was not reached. The 9-month DFS rate was 94.4% (95% CI, 66.6-99.2) in cohort A and 53.9% (95% CI, 15.5-81.4) in cohort C. **Conclusions:** SHR-1501 alone or in combination with BCG was well-tolerable and demonstrated a favorable efficacy in BCG-naive and BCG-unresponsive high-risk NMIBC pts, supporting further investigations. Clinical trial information: NCT05410730. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

Results of BH011 after intravesical administration in patients with CIS and/or papillary non-muscle invasive bladder cancer (NMIBC) after BCG failure: Interim results from a phase I/II clinical trial.

Dingwei Ye, Xiaolin Lu, Hailong Hu, Mingde Lei, Zhisong He, Kaiwei Yang, Zihan Xue, Ning Kang, Qun Sun, Xiaohua Wei; Fudan University Cancer Hospital, Xuhui, Shanghai, China; Department of Urology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Second Affiliated Hospital of Tianjin Medical University, Tianjin, China; The Second Hospital of Tianjin Medical University, Tianjin, China; Peking University First Hospital, Beijing, China; Department of Urology, Peking University First Hospital; The Institution of Urology, Peking University; Beijing Key Laboratory of Urogenital Diseases (Male) Molecular Diagnosis and Treatment Center; National Urological Cancer Center, Beijing, China; Zhuhai Beihai Biotech Co, Ltd, Zhuhai, China

Background: Treatment options are limited for patients (pts) with high risk NMIBC (HR NMIBC) after BCG failure. BH011 is a novel docetaxel formulation for intravesical administration that significantly increased the concentration of free docetaxel and bladder tissue permeability compared to TAXOTERE, which may result in a more efficient and effective tumor response. BH011 is administered intravesically to providing durable efficacy in high-risk NMIBC while avoiding systemic toxicities. This phase I/II study evaluates the safety, preliminary efficacy of intravesical BH011 in pts with HR NMIBC after BCG failure. **Methods:** This phase I/II study enrolled BCG failure (including refractory, recurrence, non-responsive, and intolerant) HR NMIBC pts. The papillary tumors should be removed all visible lesions by TURBT. The purpose of this study was to assess the preliminary efficacy under 17.5mg. Within 2-8 weeks after TURBT, eligible pts receive BH011 on day 1, once a week for 6 weeks during the induction treatment and once a month for 12 months during the maintenance treatment. The primary efficacy endpoint was 3 month Complete Response Rate (CRR). **Results:** To date, 25 pts have been treated with 17.5 mg of BH011, including 7 pts with CIS (±Ta/Ta) and 18 pts with papillary tumors alone (high-grade Ta or T1). All patients had been previously treated with BCG and failed. BH011 was well tolerated by all pts. All treatment-related adverse events (TRAE) were grade ≤ 2 and there were no TRAEs leading to discontinuation. Common TRAEs include urinary tract infection, glucosuria, proteinuria, urinary frequency, haematuria, cholesterol high, creatinine increased, and anaemia. A total of 24 evaluable pts were included in the efficacy analysis, which showed that pts had a CRR of 96% at 3 months and 71% at 12 months. RFS and PFS were analysed using the Kaplan-Meier method, and the 12-month RFS rate was 70%, with a median RFS of 20.21 months and a PFS rate of 100%. Six evaluable pts with CIS (±Ta/Ta) were analysed and the CRR was 100% (6/6) at 3 months and 83% (5/6) at 12 months. Analysis of the different pathology type subgroups and BCG failure type subgroups showed that the clinical efficacy of BH011 was independent of pathology type and BCG failure type ($P > 0.05$). **Conclusions:** Interim results show that intravesical BH011 is well tolerated and that it has strong significant and durable clinical efficacy in patients with HR NMIBC after BCG failure, particularly in pts with CIS (CRR = 100%). BH011 has the potential to have a transformative effect on the treatment landscape of NMIBC. Clinical trial information: NCT06732531. Research Sponsor: Zhuhai Beihai Biotech Co.,Ltd.

Efficacy of BH011.

Month	3	6	12
CR rate in all Pts, %	96	79	71
CR rate in CIS (±Ta/T1), %	100	83	83
RFS rate in all Pts, % (95%CI)	96 (88, 100)	79 (61, 97)	70 (45, 95)
DOR rate in all Pts, % (95%CI)	96 (87, 100)	78 (59, 97)	68 (33, 100)

AURORA: A single arm, multicentre, phase II clinical trial of atezolizumab immunotherapy for advanced squamous cell carcinoma of the bladder and urinary tract.

Simon J. Crabb, Jonathan Martin, Megan Lawrence, Mary Danh, Sarah-Jane Bibby, Denise Dunkley, Uroosha Ali, Oli Dewane, Hannah Markham, Allen Knight, Cheng Lee Chaw, Joachim Chan, Thomas Powles, Jim Barber, Constantine Alifrangis, Mark David Linch, Robert A Huddart, Alison Jane Birtle, Robert Jones Jones, Gareth Owen Griffiths; Southampton Clinical Trials Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; Primary Care and Population Health, University College London, London, United Kingdom; Southampton Clinical Trials Unit, University of Southampton, Southampton, United Kingdom; Department of Histopathology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; Action Bladder Cancer UK, Tetbury, United Kingdom; James Cook University Hospital, Middlesbrough, United Kingdom; The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom; Barts Health NHS Trust, London, United Kingdom; Velindre University NHS Trust, Cardiff, Wales; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, United Kingdom; Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom

Background: Urinary tract squamous cell carcinoma (UTSCC) is a rare disease, comprising approximately 3% of histological subtypes from the bladder and urinary tract. Limited data exist to support treatment choices and no prospective trials, dedicated specifically to this histology, have been undertaken to evaluate immunotherapy. Prior data indicate high PD-L1 expression and tumour immune cell infiltration in a proportion of UTSCC cases. We report the Stage 1 outcome for the AURORA clinical trial, which tested atezolizumab immunotherapy for patients with incurable UTSCC. **Methods:** Patients had progressive, measurable, UTSCC and ECOG performance status 0-2. Mixed histology was permitted but with no urothelial carcinoma component. One prior line of systemic chemotherapy was permitted for advanced disease but no prior immunotherapy. Treatment comprised atezolizumab (1680 mg IV, q28d) until disease progression and for up to one year if tolerated. The primary endpoint was best overall objective response rate (ORR; RECIST v1.1) with a Simon 2 stage statistical design, and planned, independent, interim efficacy review after 19 patients were assessable for response (without a recruitment pause). If ≥4 of the first 19 patients (Stage 1) achieved an objective response (confirmed partial or complete response), then recruitment would continue through Stage 2, where ≥8 responses in 33 patients were required to indicate further investigation was warranted (p1 = 15%, p2 = 35%, 1-sided alpha = 0.1, power = 90%). Secondary endpoints included progression free survival (PFS), overall survival (OS), duration of response, safety and tolerability (CTCAEv5). **Results:** 3 of the first 19 recruited patients achieved an objective response (15.8%, 95% confidence interval (CI) 3.4 - 39.6; 3 partial and no complete responses) leading the Independent Data Monitoring Committee to recommend closure to recruitment. 3 further patients (15.8%) achieved a best response of stable disease. With a median duration of follow up of 10.1 months (95% CI 3.5 - not calculated), 17 PFS events have occurred, with a median PFS of 3.0 months (95% CI 1.4 - 3.8). 13 patients have died, with a median OS of 5.2 months (95% CI 2.7 - 8.5). Duration of objective response was 8.4 months in one patient and is ongoing in the other 2 responding patients. Adverse events were predominantly disease related. Atezolizumab was well tolerated with no new safety signals observed relating to this treatment. **Conclusions:** The objective response rate, and other efficacy endpoints, did not meet protocol defined thresholds for activity and so do not support further development of atezolizumab immunotherapy as a monotherapy for unselected patients with UTSCC. Translational endpoint analyses are ongoing. Clinical trial information: ISRCTN83474167. Research Sponsor: Cancer Research UK; CRCPJT\100018; Roche Products Ltd.

Prevalence of histology-agnostic biomarkers in pure squamous cell carcinomas of the genitourinary tract.

Saad Omar Atiq, Dilara Akbulut, Shayan S. Nazari, Elias Chandran, Nicholas I. Simon, Andre Rashad Kydd, Giovanni Maria Iannantuono, Salah Boudjadi, Abdul Rouf Banday, Maria Merino, Raju Chelluri, Sandeep Gurram, Norm Smith, Andrew Elliott, Andrea B. Apolo; Genitourinary Malignancies Branch, CCR, NCI, NIH, Bethesda, MD; Laboratory of Pathology, CCR, NCI, NIH, Bethesda, MD; Caris Life Sciences, Phoenix, AZ; National Cancer Institute, Bethesda, MD; Fondazione Policlinico Universitario Agnostino Gemelli, Roma, Italy; National Institute of Health, Bethesda, MD; National Institutes of Health (NIH), Bethesda, MD; National Cancer Institute, National Institutes of Health, Bethesda, MD; Caris Life Sciences, Irving, TX

Background: Pure squamous cell carcinomas (SCC) of the genitourinary (GU) tract are less responsive to chemotherapy with limited therapeutic options for systemic disease. SCCs account for 2-8% of bladder cancer cases and treatment mirrors urothelial carcinoma despite significantly lower responses. There are 8 FDA-approved histology-agnostic treatments based on biomarker profiling: dostarlimab (dMMR/MSI-H), pembrolizumab (dMMR/MSI-H; TMB-H), larotrectinib (NTRK fusion), entrectinib (NTRK fusion), selpercatinib (RET fusion), trastuzumab deruxtecan (HER2 positive), and dabrafenib plus trametinib (BRAF V600E mutation). Data are limited on gene alterations associated with SCC of the GU tract. This study aimed to explore the prevalence of biomarkers in pure SCCs of the GU tract. **Methods:** A retrospective analysis was performed to identify bladder cancer patients with SCCs of the GU tract that underwent comprehensive molecular profiling. Cases were reviewed by a GU pathologist to confirm pure SCC, and biomarker profiling was conducted to assess prevalence of markers with available histology-agnostic treatments as well as areas of potential future exploration through clinical trials. NextGen DNA sequencing (592-gene panel or whole exome) was performed at Caris Life Sciences (Phoenix, AZ). **Results:** Of 8000 bladder cancer cases, 655 (8.2%) were coded as having components of SCC. After excluding mixed histologies, 275 (2.4%) cases were reviewed by a GU pathologist, and 169 (2.1%) cases of pure SCC of the GU tract were identified. Of these, 88 were females (51.1%) and 81 males (47.9%), with a median age of 70 (range 34-89). Of the histology-agnostic biomarkers with FDA approvals, 45 patients (27%) were TMB-H and 2 patients (1%) harbored dMMR/MSI-H status. No patients harbored *NTRK* fusions, *RET* fusions, or *BRAF* V600E mutations. HER2 IHC data were not available for cases, but *ERBB2* mutation was present in 4 patients (2%) and 1 patient (0.6%) had ERBB2 amplification. Other notable mutations included *TP53* (70%), *pTERT* (64%), *PIK3CA* (30%), *CDKN2A* (22%), *FAT1* (19%), *KDM6A* (10%), *FGFR3* (5%), and *PTEN* (5%). HRD-associated mutations included *BRCA1* (2%), *BRCA2* (4%), *ATM* (4%), *PALB2* (1%), *CHEK2* (2%), *RAD51* (1%), and *BRIP1* (1%). *AKT* mutation was present in 2% of patients. *BAP1* was mutated in 3% of patients. Six of 20 (30%) patients were P16+ by IHC. No significant difference in mutation prevalence was observed between specimens from bladder tumors and metastatic sites. **Conclusions:** This study provides a comprehensive analysis of the genetic landscape of pure SCC of the GU tract that may inform future therapeutic strategies for this rare tumor with limited treatment options. Almost one-third of patients were TMB-High, reflecting a population that may benefit from immune checkpoint inhibitors monotherapy or combination strategies. Other histology-agnostic targets for current therapies were relatively infrequent. Research Sponsor: None.

Sasanlimab in combination with bacillus Calmette-Guérin (BCG) in BCG-naive in BCG-naive, high-risk non–muscle-invasive bladder cancer (NMIBC): Patient-reported outcomes (PROs) from CREST.

Jens Bedke, Neal D. Shore, Thomas Powles, Matthew D. Galsky, Joan Palou, Daniel R. Saltzstein, Félix Guerrero-Ramos, Motonobu Nakamura, Tilman Todenhöfer, Raj Satkunasivam, Peter Colin Black, Julia Brinkmann, Jane Chang, Anthony Eccleston, Arlene Reisman, Jennifer Vermette, Gary D. Steinberg; Department of Urology & Eva Mayr-Stihl Cancer Center, Stuttgart, Germany; Carolina Urologic Research Center, Myrtle Beach, SC; Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, United Kingdom; The Tisch Cancer Institute, Mount Sinai, New York, NY; Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain; Urology San Antonio, San Antonio, TX; University Hospital 12 de Octubre, Madrid, Spain; Department of Urology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; Studienpraxis Urologie, Nürtingen, Germany; Department of Urology, Houston Methodist Hospital, Houston, TX; Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; Pfizer Pharma GmbH, Berlin, Germany; Pfizer Inc., New York, NY; Pfizer Ltd, Tadworth, United Kingdom; Pfizer, Inc., Cambridge, MA; Department of Urology, Rush University, Chicago, IL

Background: Sasanlimab with BCG (induction [IND] + maintenance [MNT]) significantly improved investigator-assessed EFS vs BCG (IND + MNT) and had a manageable safety profile in patients (pts) with BCG-naive, high-risk NMIBC in the phase 3 CREST study primary analysis. We report PRO data not previously presented from CREST for Arms A and C assessing the impact of sasanlimab with BCG on QOL. **Methods:** Eligible pts were randomized 1:1:1 to receive sasanlimab with BCG (IND + MNT; Arm A), sasanlimab with BCG (IND; Arm B), or BCG (IND + MNT; Arm C). PROs were secondary endpoints and not included in the testing hierarchy. PROs were assessed prior to first dose (baseline [BL]), and at scheduled visits until an event or end of treatment (every 4 wk until Wk 28, every 12 wk until Wk 100) and at disease follow-up using the EORTC QLQ-C30 and QLQ-NMIBC24. Longitudinal mixed effect-model analyses were used to assess change from BL in the EORTC QLQ-C30 and NMIBC24 items. **Results:** At data cutoff (Dec 2, 2024), 695/703 pts randomized to Arms A (n = 348) and C (n = 347) had a BL score and ≥1 post-BL score. Completion rates were > 84% for all visits through the end-of-treatment visit (Cycle 25). QLQ-C30 Global Health Score QOL scores were numerically similar between arms (mean difference: −2.345; 95% CI: −4.058, −0.632; P = 0.007). No clinically meaningful differences (≥10-point change; Osoba et al. JCO 1998) were observed across urinary symptoms (NMIBC24; mean difference: 0.851; 95% CI: −1.030 , 2.731; P = 0.375), intravesical treatment issues (NMIBC24; mean difference: 1.271; 95% CI: −0.587, 3.130; P = 0.180), and EORTC QLQ-C30 items (Table) between arms, except in a small sample for female sexual problems (NMIBC24; mean difference: 18.502; 95% CI: 6.228, 30.775; P = 0.007). Results were statistically significant but not clinically meaningful. **Conclusions:** PROs from CREST showed QOL was maintained when combining sasanlimab with BCG vs BCG (both IND + MNT). These results can help inform the benefit-risk assessment of CREST. Clinical trial information: NCT04165317. Research Sponsor: Pfizer Inc.

	Arm AEstimated mean (95% CI) n=348	Arm CEstimated mean (95% CI) n=347	Estimated mean difference (95% CI)	P value
Physical functioning	−2.485(−3.493, −1.477)	−0.261(−1.272, 0.750)	−2.224(−3.651, −0.796)	0.002
Role functioning	−4.836(−6.187, −3.484)	-0.910(−2.265, 0.445)	−3.926(−5.840, −2.012)	0.000
Emotional functioning	0.074(−1.046, 1.194)	2.071(0.948, 3.194)	−1.997(−3.583, −0.411)	0.014
Cognitive functioning	−2.137(−3.174, −1.101)	−0.832(−1.872, 0.208)	−1.305(−2.774, 0.163)	0.081
Social functioning	−3.863(−5.111, −2.615)	−0.415(−1.666, 0.836)	−3.448(−5.215, −1.681)	0.000
Fatigue	4.881(3.488, 6.274)	1.211(−0.185, 2.607)	3.670(1.698, 5.642)	0.000
Nausea and vomiting	0.908(0.473, 1.343)	0.545(0.108, 0.982)	0.363(−0.253, 0.980)	0.248
Pain	2.784(1.519, 4.048)	−0.174(−1.443, 1.095)	2.958(1.166, 4.749)	0.001

TPS4611 Poster Session

STARLITE-1: 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, Rebecca Slack Tidwell, Hyunsoo Hwang, Roserika Brooks, Lauren Michelle Wood, Travis Solley, Dahlia Mack, Yuko Yamamura, Aradhana M. Venkatesan; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Nuclear Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Complete response (CR) is a rare event in advanced clear cell renal cell carcinoma (ccRCC). The combination of nivolumab plus cabozantinib was approved for 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, CR rate was only 9%. Drugs that could synergize with T cell anti-tumor activity can improve CR rates. Radiation-induced DNA damage to activate the cGAS-STING pathway is a promising mechanism. ^{177}Lu-girentuximab is an antibody-radioisotope that targets CAIX, a cell surface glycoprotein expressed in $>$ 95% of ccRCC. As a single agent in metastatic ccRCC, ^{177}Lu-girentuximab was safe and effective in stabilizing disease in 57% of patients. We hypothesize ^{177}Lu-girentuximab-induced DNA damage will potentiate the STING pathway, synergizing with nivolumab and cabozantinib to promote trafficking and infiltration of activated T cells and achieve higher CR rates. **Methods:** Up to 100 adults with treatment-naive, locally advanced or metastatic ccRCC, adequate organ/marrow function, and $\geq$1 measurable lesion by RECIST 1.1 will be enrolled. Patients will receive ^{177}Lu-girentuximab IV on day 1 of cycles 1, 4, and 7 (every 12 weeks) for up to 3 cycles. The starting dose of ^{177}Lu-girentuximab will be 1480 MBq/m^2 (61% of single agent maximum tolerated dose); subsequent doses in the same patient may be reduced to 1110 MBq/m^2 or 740 MBq/m^2 based on adverse events. Starting day 1 of cycle 2 (week 5), patients will receive nivolumab 480 mg IV every 4 weeks and cabozantinib 40 mg PO every day. All cycles are 28 days. A 5-patient safety lead-in will evaluate myelosuppression. The co-primary endpoints are safety and CR rate by RECIST 1.1. Secondary endpoints are ORR, PFS by RECIST 1.1, and overall survival. The sample size was chosen for reasonable operating characteristics to distinguish a desirable CR rate of 18% as better than the standard CR rate of 9%. 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 and biopsies will be obtained for single cell, spatial transcriptomics, and proteomics studies. Clinical trial information: NCT05663710. Research Sponsor: Telix Pharmaceuticals; DOD Kidney Cancer Research; W81XWH-22-1-0456.

TPS4612 Poster Session

STARLITE 2: Phase 2 study of nivolumab plus ^{177}lutetium-labeled anti–carbonic anhydrase IX (CAIX) monoclonal antibody girentuximab (^{177}Lu-girentuximab) in patients with advanced clear cell renal cell carcinoma (ccRCC).

Darren R. Feldman, Robert J. Motzer, Andrea Knezevic, Martin H. Voss, Serge K. Lyashchenko, Hijin Park, Steven M. Larson, Neeta Pandit-Taskar; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY; Memorial Sloan Kettering Cancer Center and Weill Medical College, New York, NY

Background: CAIX is a cell surface glycoprotein expressed in > 95% of ccRCC but rarely in normal tissues. Radiolabeling girentuximab, a CAIX-targeting monoclonal antibody, with ^{177}Lu has shown promise as a therapeutic agent in ccRCC. Targeted delivery of radiation to ccRCC cells may prime the immune response, providing rationale for combining ^{177}Lu-girentuximab with nivolumab. This phase 2, open-label, single arm study will evaluate ^{177}Lu-girentuximab in combination with nivolumab in patients with previously treated ccRCC. **Methods:** Eligible patients have locally advanced unresectable or metastatic ccRCC, ≥1 prior line of therapy (including ≥1 anti-PD-1 or anti-PD-L1 antibody), adequate organ function, and ≥1 evaluable lesion as defined by RECIST 1.1 on ^{89}Zr-girentuximab PET/CT. Patients will receive ^{177}Lu-girentuximab (max 3 cycles; IV on day 1 of cycles 1, 4, and 7) and nivolumab (240mg IV q2 weeks starting cycle 1 day 15) until disease progression or unacceptable toxicity. FDG-PET and CT CAP will be performed prior to cycles 1, 4, and 7, and then q12 weeks. All cycles are 28 days. Patients will be evaluated in a 24-week safety lead-in phase followed by an expansion phase. In the safety lead-in phase, the primary endpoint of maximum tolerated dose (MTD) of ^{177}Lu-girentuximab in combination with nivolumab will be determined with a 3+3 design using a starting dose of 1804 MBq/m^2 (75% of single agent MTD). Based on dose limiting toxicities (DLTs), the starting ^{177}Lu-girentuximab dose will be either escalated to 2405 MBq/m^2 (cohort 2; single agent MTD) or de-escalated to 1353 MBq/m^2 (cohort -1) for the next cohort. Due to expected cumulative myelosuppression, each subsequent ^{177}Lu-girentuximab dose given to the same patient will be reduced by 25% (dose 2 = 75% of dose 1; dose 3 = 75% of dose 2). In the expansion phase, a Simon 2-stage optimal design will be used to evaluate the primary endpoint of best objective response rate by RECIST 1.1 within 24 weeks. With ≥1 response in the first Simon stage of 10 patients (includes patients treated at MTD during safety lead-in), a second stage will open (n = 19) for a total of 29 patients. The regimen will be considered worthy of further study if there are ≥4 responses in the 29 patients. Secondary endpoints include PFS, OS, and safety. Exploratory imaging with ^{89}Zr-girentuximab PET/CT will be performed at baseline and before each ^{177}Lu-girentuximab dose with results correlated with RECIST response on conventional imaging. In addition, whole body planar and SPECT imaging will be performed after each ^{177}Lu-girentuximab dose to evaluate distribution, lesion uptake, and dosimetry. The prespecified number of DLTs was exceeded in cohort 2 such that dosing reverted back to 1804 MBq/m^2, in which accrual is ongoing. Clinical trial information: NCT05239533. Research Sponsor: Telix Pharmaceuticals.

TPS4613 Poster Session

A phase 1/2 first in human study of ADI-270, an armored allogeneic anti-CD70 chimeric antigen receptor γδ T cell therapy, in relapsed or refractory (R/R) clear cell renal cell carcinoma (ccRCC).

Sumanta Kumar Pal, Benjamin Garmezy, Helen Budworth, Xiaoyan Du, Shon Green, Kevin Nishimoto, Jackie Kennedy-Wilde, Blake T. Aftab, Julia D. Maltzman, Gregory Sumpao Vosganian, Brian I. Rini; Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA; Sarah Cannon Research Institute, Nashville, TN; Adicet Bio, Redwood City, CA; Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

Background: CD70 is a type II transmembrane protein of the tumor necrosis factor superfamily normally transiently expressed in activated lymphocytes, including B, T, NK, and mature dendritic cells. CD70 is aberrantly expressed in solid and hematologic cancers and is implicated in enhanced growth, metastasis, immune evasion, and suppression. In ccRCC, CD70 expression is increased in the tumor microenvironment and on malignant cells. Despite advancements in the treatment of patients with metastatic RCC, the 5-year survival rate is 15% and there remains an unmet need. ADI-270 is an investigational, allogeneic, CD70-targeting (CD27 receptor-based) Vδ1 γδ chimeric antigen receptor (CAR) T cell product expressing a dominant negative form of the TGFβ receptor II (dnTGFβRII) to mitigate the immunosuppressive effects of TGFβ within the tumor microenvironment. γδ T cells possess innate and adaptive immunity, a natural role in immune surveillance, and the ability to home to tissues. γδ T cells are ideal for an allogeneic cell therapy as their TCR recognizes MHC-independent antigens, thereby avoiding the risk of graft versus host disease. ADI-270 has demonstrated potent preclinical activity against CD70 expressing hematological and solid tumors expressing a range of CD70 levels both in vitro and in mouse xenograft models. Furthermore, ADI-270 demonstrated superior activity against tumors expressing low levels of CD70 when compared to scFv-based αβ CAR T cell benchmarks currently in clinical development. **Methods:** ADI-202427001 (NCT06480565) is a multi-center, phase 1 / 2 open-label, dose-escalation and -expansion study evaluating ADI-270 in adult patients with R/R ccRCC. Selected inclusion criteria include confirmed diagnosis of R/R advanced/metastatic ccRCC, previous treatment with an immune checkpoint inhibitor and a VEGF inhibitor, and Karnofsky performance status ≥ 70. Selection exclusion criteria include receipt of CD70 targeting treatment and autoimmune disease requiring systemic immunosuppressive therapy. Objectives of phase 1 include characterizing the safety and tolerability of ADI-270, identifying the recommended phase 2 dose (RP2D), and assessing cellular kinetics (CK), immunogenicity, pharmacodynamics (PD), and anti-tumor activity. Objectives of phase 2 include characterizing the anti-tumor activity, safety, immunogenicity, CK, and PD profile of ADI-270 at the RP2D. The totality of data from Phase 1 will be used to determine the RP2D for the Phase 2 part of the study. Responses will be evaluated per the RECIST 1.1 criteria. Additional efficacy analyses include duration of response, progression-free survival, and overall survival. Enrollment in study ADI-202427001 is ongoing. Clinical trial information: NCT06480565. Research Sponsor: AdicetBio, Inc.

TPS4614 Poster Session

A phase 1b, open-label, safety, tolerability, and efficacy study of HC-7366 in combination with belzutifan in patients with advanced or metastatic renal cell carcinoma (NCT06234605).

Neil J. Shah, Manojkumar Bupathi, Rana R. McKay, Benjamin Garmezy, Joel Picus, Moshe C. Ornstein, Robert A. Figlin, Elaine T. Lam, Edward Paul Gelmann, Hans J. Hammers, Brian H. Rank, Song Zhao, Pedro C. Barata, Mohamad Adham Salkeni, Yusra F. Shao, Scott S. Tykodi, Thomas E. Hutson, Michael Jon Chisamore, Jose Luis Iglesias, Robert J. Motzer; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Rocky Mountain Cancer Centers, Littleton, CO; University of California San Diego, San Diego, CA; Sarah Cannon Research Institute, Nashville, TN; Washington University in St. Louis, St. Louis, MO; Cleveland Clinic, Cleveland, OH; Cedars-Sinai Medical Center, Los Angeles, CA; University of Colorado Cancer Center, Aurora, CO; University of Arizona, Tucson, AZ; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; HealthPartners, Minneapolis, MN; Swedish Cancer Institute, Seattle, WA; University Hospitals Seidman Cancer Center, Cleveland, OH; Virginia Cancer Specialists, Fairfax, VA; Barbara Ann Karmanos Cancer Institute, Detroit, MI; University of Washington and Fred Hutchinson Cancer Center, Seattle, WA; Texas Tech University Health Science Center, Lubbock, TX; Department of Clinical Development, Merck & Co., Inc., Rahway, NJ; APEX Oncology Consulting, Inc., Oakville, ON, Canada

Background: HC-7366 is a novel, highly selective and potent activator of general control nonderepressible 2 (GCN2) kinase, a core regulator of metabolic stress through activation of the integrated stress response (ISR). Prolonged or hyper-activation of GCN2 suppresses general protein synthesis and induces cell cycle arrest, ultimately leading to apoptosis. HC-7366 decreases HIF expression in tumor and immunosuppressive myeloid cells and inhibits glycolysis, oxidative phosphorylation, and TCA cycle function in tumor cells. In CDX RCC xenografts, HC-7366 combined with belzutifan (BLZ) exhibited tumor regression, and in BLZ-resistant PDX models, HC-7366 demonstrated monotherapy (mono) antitumor activity. These preclinical effects of HC-7366 suggest potential therapeutic benefit in clear cell renal cell carcinoma (ccRCC) and rationale for combinations with HIF2α antagonists. Mechanism of action studies identified biomarkers of pathway engagement which may be predictive of efficacy (Stokes, AACR 2024, Abstract 4615). HC-7366 75 mg was determined to be the maximum tolerated dose (MTD) in a previous phase 1a study in patients (pts) with solid tumors which did not include ccRCC (*data on file with sponsor*). **Methods:** This is a multicenter, open-label, phase 1b dose escalation and expansion study evaluating safety, tolerability, MTD, recommended phase 2 dose (RP2D) of HC-7366 + BLZ (combo) in pts with advanced / metastatic RCC, predominantly clear cell histology. Additionally, HC-7366 60 mg mono (up to 20 patients) is assessed in parallel. In dose escalation, HC-7366 (20, 40, 60 mg po qd) + BLZ (120 mg po qd) is evaluated using a modified Toxicity Probability Interval design in up to 20 pts. Dose expansion will evaluate two HC-7366 doses selected from escalation + BLZ (15 pts/dose level). Tumor response will be assessed by CT scans every 8 wks (RECIST v1.1). Secondary endpoints include ORR, DOR, TTR, DCR, PFS, and OS. PK data will be profiled, and exploratory objectives include pharmacodynamic marker evaluation in tumor biopsies and peripheral blood samples. Key eligibility criteria include 1-3 prior therapies for the combo cohorts (naïve to BLZ/ HIF-2α inhibitors) and 1-4 prior therapies for the mono cohort (may include BLZ/ HIF-2α inhibitors), >1 measurable lesion, and willingness to provide biopsy or archival tumor samples at two timepoints. Escalation Dose levels 1 and 2 of the combination cohorts have been cleared and enrollment is ongoing for Dose level 3 (60 mg + BLZ), Expansion Dose Level 1 (40 mg + BLZ) and the mono cohort (60 mg HC-7366) at 20 US sites. The trial is sponsored by HiberCell, Inc. in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Sponsor contact: Paulette Mattson pmattson@hibercell.com, 651.312.5831. Clinical trial information: NCT06234605. Research Sponsor: None.

TPS4615 Poster Session

Transforming kidney cancer treatment through AI-enabled functional precision medicine: The PEAR-TREE2 trial.

Matthew Williams, Ekaterini Boleti, Victoria Ford, Steve Bromage, Omi Parikh, Naveen Vasudev, Eleonora Peerani, Elli Tham, Francesco Iori, Keqian Nan, Jonathan Ient, Thomas David Laurent Richardson, Nourdine Kabirou Bah, Farah Sangkolah, George Richard Tiger Bevan de Fraine, Kerrie Loughrey, Duleek Nimantha Bandara Ranatunga, Maxine Gia Binh Tran; Ourotech Ltd t/a Pear Bio, London, United Kingdom; Royal Free London NHS Foundation Trust, London, United Kingdom; Royal Devon University NHS Foundation Trust Hospital, Exeter, United Kingdom; Stepping Hill Hospital, Stockport, United Kingdom; Royal Preston Hospital, Preston, United Kingdom; St. James's Hospital, Leeds, United Kingdom; Ourotech (t/a Pear Bio), London, United Kingdom

Background: Advanced renal cell carcinoma (RCC) presents a significant clinical challenge, with limited predictive biomarkers for treatment response. Pear Bio's innovative platform utilizes 3D immune-microtumors and computer vision to predict therapeutic responses using patient-derived tumor and blood samples. This study builds upon the initial PEAR-TREE trial, aiming to validate the platform's predictive capabilities for systemic therapies, including immune checkpoint inhibitors and tyrosine kinase inhibitors, in advanced RCC. **Methods:** PEAR-TREE2 (NCT06264479) is a multicenter, observational trial conducted in the UK and US, enrolling up to 200 patients with metastatic RCC. Participants must provide fresh tumor biopsies and blood samples prior to initiation of the next line of systemic therapy. Samples are cultured in Pear Bio's platform, which uses time-lapse microscopy and AI-driven computer vision analysis to assess functional metrics including viability, cell killing, migration, culture size, immune infiltration and clustering. Predictive metrics for overall response rate (ORR) based on RECIST 1.1 criteria are the primary endpoints. Secondary objectives include predictive accuracy for progression-free survival (PFS), durable response rates, and overall survival (OS). Exploratory analyses will evaluate molecular biomarker correlations (e.g. protein expression of therapeutic target, cell subpopulation analysis, etc.) and subgroup dynamics. Statistical methods include Receiver Operating Characteristic (ROC) curve analysis and subgroup logistic regression. Patient enrollment commenced in June 2024, with interim analyses planned after 50 and 100 enrollments. Eligibility criteria include patients aged ≥18 years with advanced RCC eligible for systemic therapy. Exclusion criteria comprise early-stage RCC, patients who have commenced treatment, or non-RCC diagnoses. Additional core needle biopsies (minimum 4x 18G cores) and blood samples (40 mL) are mandatory. Recruitment is ongoing at 7 trial sites, with a target duration of 4.5 years. This novel assay could fill the gap in predictive biomarkers by enabling personalized therapy selection. By validating its patient stratification potential, the study paves the way for interventional trials, with the promise of optimizing treatment regimens and improving outcomes for kidney cancer patients. We have ongoing trials in other high-unmet-need indications including early-stage breast cancer (NCT05435352), metastatic breast cancer (NCT06182306) and gliomas (NCT06038760) hoping to revolutionize precision oncology via improved treatment selection. Clinical trial information: NCT06264479. Research Sponsor: Ourotech (t/a Pear Bio).

TPS4616 Poster Session

A randomized trial of radium-223 dichloride and cabozantinib in patients with advanced renal cell carcinoma (RCC) with osseous metastases (RADICAL/Alliance A031801).

Chinmay Jani, Heather Jacene, Pamela J. Atherton, Archana Ajmera, Tyler Zemla, Ronald C. Chen, Atish Dipankar Choudhury, Joshua Michael Lang, Suzanne Cole, Tareq Al Baghdadi, Young Kwok, Alan Tan, Himisha Beltran, Michael J. Morris, Matthew D. Galsky, Jonathan E. Rosenberg, Daniel J. George, Toni K. Choueiri, Rana R. McKay; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA; Mayo Clinic, Rochester, MN; University of California, San Diego, La Jolla, CA; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; University of Kansas Medical Center, Kansas City, KS; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; University of Wisconsin Carbone Cancer Center, Madison, WI; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; IHA Hematology Oncology Consult, Ypsilanti, MI; University of Maryland Medical Center, Baltimore, MD; Rush University Medical Center, Chicago, IL; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Department of Medical Oncology, New York, NY; Duke University Cancer Institute, Durham, NC; University of California, San Diego, CA

Background: Osseous metastases (OM) occur in approximately 30% patients with advanced RCC. Despite therapeutic advances, OM are associated with poor survival and risk of symptomatic skeletal events (SSEs). Cabozantinib targets multiple tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors and MET (Mesenchymal-Epithelial Transition factor), which are overexpressed in OM, contributing to cabozantinib's enhanced bone activity. Radium-223, an alpha-emitting bone-seeking radioisotope, prolongs survival in men with metastatic castration-resistant prostate cancer to the bone. Building on this therapeutic approach targeting OM, our pilot study of radium-223 with VEGF inhibition in RCC with OM has also shown safety, improvement in circulating bone turnover markers, and early efficacy (McKay et al, CCR 2018). To address the unmet need to improve SSE rates and outcomes in RCC and OM, we designed a study investigating cabozantinib with or without radium-223 in patients with RCC with OM (NCT04071223). **Methods:** This is an open-label, multicenter randomized phase-2 study. Key inclusion criteria include metastatic RCC of any histology with $\geq$1 OM, at least 1 OM without prior radiation, any number of prior therapies, and Karnofsky performance status $\geq$ 60%. Use of a bone protecting agent is required unless contraindicated. Patients are randomized 1:1 to cabozantinib with (Arm A) or without (Arm B) radium-223. The starting dose of cabozantinib for Arm A is 40 mg by mouth daily to be escalated to 60 mg daily after cycle 1 (1 cycle = 28 days) if no persistent grade 2 or grade $\geq$3 toxicity. Radium-223 is administered at a fixed dose of 1.49 microcurie/kg IV every 28 days x 6 doses. The starting dose for cabozantinib in Arm B is 60 mg daily. The primary endpoint is SSE-free survival. Secondary endpoints include safety, progression-free survival, overall survival, time to first SSE, objective response rate, time to subsequent anti-cancer therapies, quality of life (QoL) measures, and correlative analyses including liquid biopsy and tumor tissue analysis. The study is designed to have 85% power to detect an improvement in 6-month SSE-free survival rate from 65% to 78% with one-sided α = 0.05 significance. To ensure 124 evaluable patients, target accrual is 134 (67 per arm). The group-sequential design includes a safety run-in and an interim analysis for futility when 50% of the expected number of events have been observed. The safety run-in, performed in the first 12 patients randomized to combination therapy, did not demonstrate dose limiting toxicities. Final data analysis will occur when 99 events have been observed. The study was activated in July 2020 and accrual is ongoing throughout the National Clinical Trials Network (NCTN). Continued site participation and enrollment are essential to evaluate this therapeutic strategy. Clinical trial information: NCT04071223. Research Sponsor: None.

TPS4617 Poster Session

Clinical effectiveness of urine DNA for minimal residual disease (MRD) monitoring of urothelial carcinoma in urine: A multicenter, prospective, observational study.

Xuanjun Guo, Lei He, Kaiwei Yang, Han Hao, Wei Yu, Yanqing Gong, Zhisong He, Cuijian Zhang; Peking University First Hospital, Beijing, China; Department of Urology, Peking University First Hospital, Beijing, China

Background: Limited methods and poor compliance are major issues in urothelial carcinoma (UC) surveillance. Non-invasive monitoring of minimal residual disease (MRD) using urine tumor DNA (utDNA) represents a significant advancement, potentially reducing reliance on invasive cystoscopy and low-sensitivity imaging. Preclinical studies have demonstrated the utDNA multidimensional bioinformatic algorithm's high sensitivity (92.8%) and specificity (96.0%) by integrating copy-number variations (CNVs) and genetic mutations, showcasing its potential to improve cancer detection accuracy. However, large prospective clinical trials validating its clinical utility in postoperative recurrence and treatment efficacy monitoring remain scarce. Clinically, UC patients with similar manifestations and pathology often show divergent outcomes. Accurately assessing recurrence risk, metastasis, and treatment efficacy is an urgent need. This study aims to validate the clinical utility for recurrence monitoring and efficacy assessment in larger cohorts. **Methods:** This multicenter, prospective, observational trial evaluates the algorithm's efficacy in MRD detection among UC patients. The trial design incorporates stratification by clinical stage, including non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and upper tract UC (UTUC). We divided the study population into four cohorts: Cohort 1 includes patients with high-risk UTUC (pT3-4 or N+) who have undergone surgery; Cohort 2 consists of NMIBC patients after transurethral resection of bladder tumor (TURBT); Cohort 3 comprises MIBC patients scheduled for neo-adjuvant therapy; Cohort 4 includes patients assessed as complete response (CR) after standard trimodality treatment (TMT). In each Cohort, the accuracy for recurrence monitoring is evaluated using cystoscopy ± biopsy/surgical pathology, combined with imaging (CT/MRI) as the gold standard. Morning urine samples were collected from patients who had met the eligibility criteria and volunteered to participate in the study. Next-generation sequencing (NGS) was carried out on cell-free urinary DNA (ucfDNA) and urinary exosomal DNA (uexDNA). The minimal residual disease (MRD) score was computed by the algorithm, developed based on a feature matrix incorporating genetic alterations and copy number variations (CNVs). A classification threshold of 60 was established for clinical decision-making in the context of this study. We planed to enroll a total of 400 patients in this study. The sample sizes for the four cohorts were as follows: 100 for cohort 1, 200 for cohort 2, 50 for cohort 3, and 50 for cohort 4. As of January 2025, enrollment is ongoing, with cohorts actively monitored. The study was registered under ChiCTR2400081246. Reference: DOI: 10.1186/s12943-023-01729-7. Clinical trial information: ChiCTR2400081246. Research Sponsor: Peking University First Hospital High Quality Clinical Research Specialization.

TPS4618 Poster Session

A phase 2, open-label, randomized study of livmoniplimab in combination with budigalimab versus chemotherapy in patients with metastatic urothelial carcinoma.

Terence W. Friedlander, J. Thaddeus Beck, Eli Rosenbaum, Avivit Peer, Shingo Hatakeyama, Nadine Jahchan, Cathy Zhou, Cristiano Ferlini, Sujata Jha, Duyen Andrina Ngo, Matthew D. Galsky; University of California, San Francisco Medical Center, San Francisco, CA; Highlands Oncology, Springdale, AR; Department of Oncology, Rabin Medical Center, Petah Tikva, Israel; Rambam Health Care Campus, Haifa, Israel; Hirosaki University Hospital, Hirosaki, Japan; AbbVie, Inc., North Chicago, IL; The Mount Sinai Hospital, Mount Sinai School of Medicine, New York, NY

Background: Urothelial carcinoma (UC) has a high mortality rate in patients (pts) with metastatic disease. While immune checkpoint inhibitors (CPI), including programmed cell death protein 1 (PD-1) inhibitors combined with chemotherapy (CTx) or enfortumab vedotin (EV), have been approved for first-line treatment of metastatic (m)UC, many pts have de novo or develop acquired resistance. For pts without response to frontline treatment or whose disease has progressed on prior CPI combinations, optimal treatment is unclear and new therapies are urgently needed. Glycoprotein A repetitions predominant (GARP) is a membrane-bound receptor that complexes with latent transforming growth factor (TGF)-β1; the release of active TGF-β1 from this complex suppresses antitumor responses. Livmoniplimab (livmo), an antibody targeting the GARP:TGF-β1 complex, prevents release of active TGF-β1, thereby promoting antitumor activity. A first-in-human phase 1 study (NCT03821935) demonstrated that combining livmo and the anti–PD-1 mAb budigalimab (budi) resulted in a manageable safety profile and promising antitumor activity in pts with PD-1–refractory advanced UC (J Clin Oncol 2024;42[suppl 4]: abs 617). Herein, we describe the phase 2 study that is evaluating livmo + budi vs CTx in pts with mUC (NCT06632951). **Methods:** This multicenter, open-label, randomized study is enrolling pts aged ≥18 years who have mUC, measurable disease per RECIST v1.1, ECOG PS 0–1, and have experienced disease progression on anti–PD-1 or anti–PD-1 ligand 1 therapy. Platinum (Pt)-eligible pts must have received a Pt-containing regimen; pts who can receive EV must have experienced disease progression on/after receiving EV treatment. Primary objectives are to identify the recommended phase 3 livmo dose in combination with budi and evaluate overall survival. Secondary objectives include evaluating progression-free survival, best overall response of complete or partial response, duration of response, and assessment of safety and tolerability, pharmacokinetics, and immunogenicity of the combination. Pts will be randomized 1:1:1 to 3 arms: 1) livmo dose 1 Q3W + budi Q3W; 2) livmo dose 2 Q3W + budi Q3W; or 3) investigator's choice of CTx (paclitaxel, docetaxel, or gemcitabine). Pts will be stratified by ECOG PS (0 vs 1) and first-line therapy (pembrolizumab + EV vs CTx). Treatment for pts in Arms 1 and 2 will continue until a maximum of 35 cycles. For pts in Arm 3, treatment will continue for the duration that is consistent with local guidelines/practice for this pt population. No crossover between arms will be permitted. For all pts, treatment is discontinued at disease progression or if other protocol-defined discontinuation criteria are met. In total, approximately 150 pts (50 pts/arm) are planned for enrollment globally. Clinical trial information: NCT06632951. Research Sponsor: AbbVie, Inc.; n/a

TPS4619 Poster Session

A phase 2/3 study of bicycle toxin conjugate zelenectide pevedotin (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 Institute, 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, Milan, Italy; Columbia University Irving Medical Center, New York, NY; Princess Margaret Cancer Centre, Toronto, ON, Canada; Sarah Cannon Research Institute, Nashville, TN; Bicycle Therapeutics, Cambridge, MA; Bicycle Therapeutics, Cambridge, United Kingdom; Yale School of Medicine, New Haven, CT

Background: Zelenectide pevedotin (zele; 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 la/mUC, and is a validated therapeutic target (Hoffman-Censits 2021). Zele 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 zele (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 zele as monotherapy, or combined with pembrolizumab (pembro), vs chemotherapy in pts with la/mUC (NCT06225596/BT8009-230; Duravelo-2). **Methods:** The trial will enroll n≤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) zele 5 mg/m^2 on days [D]1, 8, and 15 + pembro 200 mg on D1; 2) zele 6 mg/m^2 on D1 and 8 + pembro 200 mg on D1; or 3) chemotherapy (gemcitabine + cisplatin / carboplatin, followed by avelumab maintenance in appropriate patients). Cohort 2 will be randomized 1:1 to receive: 1) zele 5 mg/m^2 on D1, 8, and 15 or 2) zele 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 zele + pembro (Cohort 1) or zele monotherapy (Cohort 2) to be used for the rest of the study. An additional Cohort 2 arm, optimal dose of zele + pembro, will open after completion of the interim analysis. Treatment 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), 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**

A randomized phase 2 study of the efficacy and safety of stereotactic body radiation therapy (SBRT) in patients with metastatic urothelial carcinoma and oligoprogression on maintenance therapy with avelumab (VOLGA 2).

Ilya Tsimafeyeu, Natalia Dengina, Timur Mitin; Bureau for Cancer Research - BUCARE, New York, NY; Ulyanovsk Oncology Center, Ulyanovsk, Russian Federation; Oregon Health & Science University, Department of Radiation Medicine, Portland, OR

Background: For metastatic urothelial cancer (mUC) with multiple metastases, the standard treatment involves platinum-based chemotherapy followed by maintenance avelumab. Despite this, disease progression occurs in approximately half of patients at a median of 5.5 months, often requiring a switch to second-line therapy. The concept of oligoprogressive mUC and its optimal management remain poorly defined compared to other tumor types. The VOLGA 2 study aims to assess the preliminary efficacy and safety of SBRT in patients with mUC and oligoprogression during maintenance therapy with avelumab. **Methods:** VOLGA 2 is a randomized, prospective, multicenter phase 2 trial. Patients with histologically confirmed mUC and measurable lesions according to RECIST 1.1, undergoing avelumab maintenance therapy with extracranial oligoprogression, are randomized to receive SBRT targeting oligoprogressive lesions or to second-line therapy of the physician's choice. Oligoprogression is defined as disease progression due to the appearance of up to five new metastases or a significant increase in up to five existing lesions, with other disease sites remaining stable under ongoing systemic or local therapy. For patients in the SBRT arm, repeat SBRT to previously non-irradiated lesions is allowed and recommended if the interval between progressions exceeds four months. Patients with brain metastases and cord compression are excluded from the study. The primary endpoint is 2-year overall survival (OS) rate. Secondary endpoints include median OS and progression-free survival, overall and irradiated lesion response rates, and safety. The study will enroll 58 patients (H0 = 45%, Ha = 80%, alpha = 0.05, power = 0.8). Clinical trial information: KCRB10122024. Research Sponsor: Bureau for Cancer Research - BUCARE.

TPS4621 Poster Session

A phase II trial to evaluate clinical efficacy, pharmacodynamics and exploratory analysis of pemetrexed in relation to MLL4 and UTX alteration status in patients with relapsed/refractory metastatic urothelial carcinoma and other solid tumors.

Carolyn Moloney, Zibo Zhao, Ali Shilatifard, Joshua J Meeks, David James VanderWeele, Tarik Demir, Therese Davis Brown, Ruohui Chen, Young Kwang Chae, Aparna Kalyan, Chengwei Peng, Mary F Mulcahy, Devalingam Mahalingam; Development of Therapeutics, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Biochemistry and Molecular Genetics, Chicago, IL; Northwestern University Feinberg School of Medicine, Chicago, IL; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Developmental Therapeutics, Chicago, IL; Robert Lurie Cancer Center, Chicago, IL; Department of Statistics, Chicago, IL; Department of Medicine, Division of Medical Oncology, Northwestern University, Chicago, IL

Background: MLL4 (encoded by KMT2D) and UTX (encoded by KDM6A) are protein components of the epigenetic chromatin modifier complex COMPASS. MLL4 alterations are found in ~10% of all cancers including ~29% of bladder cancer (BLCA). UTX alterations are found in up to ~5% of all cancers including ~29% of BLCA. These alterations have not been previously therapeutically targeted as a precision oncology strategy in humans despite their frequency. We recently published the results of a CRISPR/Cas9 knockout screen in cells lacking MLL4/UTX-COMPASS function, which revealed synthetic lethality upon loss of genes that encode enzymes involved in de novo nucleotide synthesis (dnNS) [Zhao et al. J Clin Invest. 2023; Zhao et al. PNAS. 2023]. We also reported that MLL4 truncation mutations confer an inhibitor-targetable dependence on dnNS in colorectal cancer (CRC) and BLCA. We demonstrated sensitivity to lometrexol, which targets the enzyme GART (glycinamide ribonucleotide formyltransferase), in animal models of CRC and BLCA with MLL4 truncation. Our preclinical results clearly indicated the potential for dnNS inhibition as a targeted therapy for patients stratified by MLL4 or UTX status. Pemetrexed was identified as a more clinically relevant purine synthesis inhibitor for further development due to its well-established safety profile and prior use in BLCA. **Methods:** We have initiated an investigator-initiated, open-label phase II basket clinical trial at Northwestern University (NCT06630416). Patients with advanced, treatment-refractory tumors with MLL4 (KMT2D) or UTX (KDM6A) mutations (as identified by next generation sequencing) are enrolled in 2 cohorts: a) BLCA and b) other solid tumors. Other key inclusion criteria include ECOG performance status 0-2 and adequate organ function. Prior pemetrexed use is a key exclusion criterion. Patients are treated with pemetrexed 500mg/m2 IV Q 3 weeks. We intend to enroll up to 64 patients to allow for 58 evaluable patients (29 in each cohort) to achieve the null hypothesis. We will use a Simon 2-stage design, with 10 patients enrolled in each cohort in the first stage. The null hypothesis is that the true response rate is 0.1, and the alternative hypothesis is that the true response rate is 0.3. If there are 5 or more responses among these 29 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.05 and yields a power of 0.8. This clinical trial has accrued 1 patient as of January 28th, 2025. Correlative studies will be carried out alongside the study to assess for mechanisms of resistance to pemetrexed. Molecular analysis of ctDNA will be performed on plasma for both arms and for plasma and urine for cohort A (bladder cohort) at pre-determined time points during treatment. Clinical trial information: NCT06630416. Research Sponsor: Robert Lurie Cancer Center, Northwestern Memorial Hospital, Chicago, IL, 60611.

TPS4622 **Poster Session**

Adjuvant sacituzumab govitecan (SG) plus nivolumab (N) in patients (pts) with muscle-invasive urothelial carcinoma (UC) at high-risk for recurrence.

Nataliya Mar, Siamak Daneshmand, David Joseph Benjamin, Anishka D'souza, Michael A. Daneshvar, Arash Rezazadeh; University of California Irvine, Irvine, CA; Department of Urology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Hoag Family Cancer Institute, Newport Beach, CA; USC Norris Comprehensive Cancer Center, Los Angeles, CA; University of California, Irvine Health, Orange, CA; University of California, Irvine, CA

Background: Pts with muscle-invasive UC of the bladder or upper genitourinary tract who undergo radical cystectomy or nephroureterectomy are at high risk for cancer recurrence if residual pathologic advanced disease is identified at the time of surgery. Emerging data demonstrates that pts with minimal residual disease following curative-intent surgery, as detected by circulating tumor DNA (ctDNA), may be at a particularly high risk of UC recurrence. Adjuvant N has been approved post curative-intent surgery, with or without prior neoadjuvant chemotherapy (NAC), in pts with muscle-invasive UC at high risk of recurrence based on results of the CheckMate 274 study, which demonstrated a disease free survival (DFS) at 6 months of 74.9% with N versus 60.3% with placebo. SG is an antibody-drug conjugate with activity in UC. Evaluating intensification of adjuvant therapy in order to reduce the chance of metastasis development is of great interest. **Methods:** This is an IRB-approved, prospective, multi-center, single-arm phase 2 study of combination therapy with SG plus N. To be eligible, pts must have documented muscle-invasive UC, with variant and mixed histology allowed, except small cell. Pts must have undergone curative-intent surgery within 180 days prior to study therapy initiation and be radiographically free of metastasis. Pts who received prior NAC must have T2-T4 or node positive disease on surgical pathology, while those without NAC must have pathologic T3-T4 or node positive disease. Pts must also be ineligible or refuse platinum-based adjuvant chemotherapy. Additional selected eligibility criteria include creatinine clearance of at least 30 ml/min and adequate bone marrow function. If eligible for the study, pts will receive SG 7.5 mg/kg on day 1 and 8 combined with Nivolumab 360 mg on day 1 given every 21 days for 4 cycles, followed by single-agent Nivolumab 480 mg on day 1 given every 28 days for an additional 11 cycles. Use of growth factor support is allowed, as per institutional practice. Primary study endpoint is investigator-assessed DFS at 6 months. Secondary study endpoints include DFS, distant metastasis-free survival (MFS), overall survival (OS), incidence of grade 3 or higher adverse events, rate of ctDNA clearance in baseline ctDNA positive patients as well as exploratory biomarker analysis. The sample size calculation was based on a one-sided one sample test for exponential hazard rate when the probability of DFS at 6-months in the experimental group is 85% and in the historical control group is 75% in order to detect a hazard ratio of 0.565 with a power of 80% at a 0.05 significance level. Projected study accrual time is 24 months and per pt follow-up time is 36 months. Out of 23 anticipated pts, 3 have been enrolled to date since study activation in 11/2024. Clinical trial information: NCT06682728. Research Sponsor: None.

TPS4623 Poster Session

Neoadjuvant stereotactic radiotherapy and enfortumab vedotin: A phase I/II study for localized, cisplatin ineligible, muscle invasive bladder cancer (STAR-EV).

Tian Zhang, Solomon L. Woldu, Minjae Lee, Qian Qin, Suzanne Cole, Waddah Arafat, Changchuan Jiang, Jue Wang, Kevin Dale Courtney, Andrew DeVilbiss, Molly McGuire, Raquibul Hannan, Daniel X. Yang, Aurelie Garant, Isamu Tachibana, Kris Gaston, Andrew Zhuang Wang, Vitaly Margulis, Yair Lotan, Neil B. Desai; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Department of Urology, UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, TX

Background: Patients with muscle invasive bladder cancer (MIBC) may not be candidates for cisplatin-based chemotherapy based on their comorbidities and clinical status. Based on EV-103 cohort H, patients with localized, cisplatin ineligible MIBC respond well to enfortumab vedotin (EV), with 36% pathologic complete responses (pCRs). Radiation (XRT) is also an effective therapy for MIBC, with recent retrospective data showing safety when combining XRT-EV. Therefore, we designed a trial with EV and XRT to improve pCR rates. **Methods:** STAR-EV is a single center, phase 1/2 trial open at UT Southwestern Medical Center. Patients will receive EV 1.25mg/m2 IV days 1/8 every 3 weeks for 3 cycles, with either sequential or concurrent stereotactic body XRT (SBRT) in 5 fractions. The safety lead-in phase starts with SBRT given at cycle 3 day 21 and then escalated forward to start at cycle 2 day 15 (level 1) or cycle 1 day 15 (level 2). All patients undergo radical cystectomy (RC). Dose limiting toxicities during the safety portion include non-hematologic adverse events grade 3 or higher, not completing 3 cycles of EV, delaying SBRT over 2 weeks, or delaying RC over 8 weeks. Rate of pCR is the primary endpoint for efficacy, with a goal of 60% pCR. In a Simon's two-stage design, if more than 3 pCRs are seen in the first 8 patients, 11 additional patients will be enrolled (total n = 19). The null hypothesis will be rejected if more than 10 pCRs are found. Main inclusion criteria include urothelial cancer of the bladder, cT2-4aN0M0, $>$ 50% urothelial histology, and cisplatin ineligible; main exclusion criteria include any small cell/neuroendocrine histology, prior systemic therapy for bladder cancer, prior pelvic XRT, baseline grade 2 or higher neuropathy, prior allergic reaction attributed to EV, or uncontrolled intercurrent illness. Secondary endpoints include safety of combining EV and SBRT, rate of pathologic down-staging; and exploratory objectives include quality of life, disease free survival after RC, and delay of RC $>$ 8 weeks from end of EV/SBRT. Serum and urinary biomarkers will be explored. The study is open and enrolling. Clinical trial information: NCT06394570. Research Sponsor: Astellas.

TPS4624 **Poster Session**

PUNCH03: A phase II study of disitamab vedotin combined with tislelizumab and bacillus Calmette-Guerin (BCG) in Her2-positive high-risk non-muscle-invasive bladder cancer (HR NMIBC).

Zongren Wang, Bin Huang, Yukun Wu, Jiahao Lei, Lingwu Chen, Junxing Chen; Department of Urology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Disitamab vedotin (RC48) was a novel antibody drug conjugate that targets the Her2 protein. The KEYNOTE-057 study has supported the benefits of PD-1 inhibitor in HR NMIBC patients (pts). Our study was established to evaluate the efficacy and safety of RC48 combined with tislelizumab and BCG as a bladder-preserving treatment for Her2-positive HR NMIBC pts. **Methods:** This open-label phase II study enrolled BCG-naïve HR NMIBC pts with multiple papillary tumors (high-grade Ta or T1 tumors), and all pts were Her2-positive (IHC 2+ or 3+). Firstly, the papillary tumors should be removed all visible lesions by transurethral resection of bladder tumor (TURBT). Secondly, pts were administered RC48 (2.0 mg/kg, ivgtt), every 2 weeks for 1 cycle, and were administered tislelizumab (200 mg, ivgtt), every 3 weeks for 1 cycle. Then, pts received second TURBT, and pts were administered 3 cycles of RC48 (2.0 mg/kg, Q2W, ivgtt) and tislelizumab (200mg, Q3W, ivgtt). Finally, pts received 18 instillations of BCG plus at least 1 year of tislelizumab (200 mg, Q3W, ivgtt). Specifically, pts were started on an induction course of BCG with 6 instillations every week, followed by maintenance with 3 instillations every 2 weeks and 9 instillations every 4 weeks. The primary end point was recurrence-free survival (RFS) rate at 12 months. Secondary end points were bladder-preservation rate, OS and safety. Our study estimated a RFS rate at 12 months was no less than 85% and the study would enroll 38 pts. Clinical trial information: ChiCTR2400093839. Research Sponsor: None.

TPS4625 **Poster Session**

Updates to CORE-008: A phase 2 multi-arm, multi-cohort study to evaluate intravesical cretostimogene grenadenorepvec in patients with high-risk non-muscle invasive bladder cancer.

Gary D. Steinberg, Trinity Bivalacqua, Siamak Daneshmand, Neal D. Shore, Shreyas Joshi, Colin P.N. Dinney; Department of Urology, Rush University, Chicago, IL; Department of Urology, Hospitals of the University of Pennsylvania, Philadelphia, PA; Department of Urology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Carolina Urologic Research Center, Myrtle Beach, SC; Department of Urology, Emory University, Atlanta, GA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment for High-Risk Non-Muscle Invasive Bladder Cancer (HR NMIBC) includes Transurethral Resection of Bladder Tumor (TURBT) followed by intravesical Bacillus Calmette–Guérin (BCG). Despite high initial response rates, over 50% of patients will recur and 20-40% are at risk for progression. Treatment of HR NMIBC is challenged by the ongoing BCG shortage, thus there exists a need for clinically effective, well-tolerated, and readily available treatment options. Cretostimogene grenadenorepvec is an oncolytic immunotherapy with a dual mechanism of action. It selectively replicates in and lyses bladder cancer cells with Retinoblastoma (Rb)-E2F pathway alterations. The subsequent release of virus- and tumor-specific antigens initiate antitumor immune activation which is further amplified by the GM-CSF transgene. Cretostimogene received Fast Track and Breakthrough Therapy Designations by the US FDA for HR BCG-Unresponsive NMIBC with CIS indication. Given the strength of these data, the CORE-008 clinical trial (NCT06567743) was developed as a Phase 2, multi-arm, multi-cohort trial to further evaluate the efficacy and safety of cretostimogene in patients with HR NMIBC. **Methods:** Eligibility criteria: pathologic confirmation of HR NMIBC, both CIS containing and papillary only, as defined by the American Urologic Association guideline. Cohort A (BCG-naive) includes patients who have not received prior BCG. Cohort B (BCG-exposed) consists of patients who have received prior BCG and recurred at the initial clinical evaluation or at a delayed timepoint. Cohort CX, recently added, will evaluate safety and High-Grade Event-Free Survival (HG-EFS) of cretostimogene in combination with intravesical gemcitabine, either concurrent (Arm 1) or sequential (Arm 2) in BCG-exposed and BCG-unresponsive patients. The combination is believed to leverage complementary mechanisms and potential immune modulating synergy to enhance outcomes. Intravesical cretostimogene will be instilled with n-dodecyl-β-D-maltoside (DDM), an excipient that enhances adenoviral delivery, for six weekly doses during the induction phase, followed by three weekly maintenance cycles quarterly through month 12, then every six months through month 36. Re-induction is permitted. The primary endpoint for CIS is Complete Response (CR) at any time and HG-EFS for papillary-only disease. Secondary endpoints will include Duration of Response, all-cause Event-Free Survival, Bladder Cancer Specific Survival, Cystectomy-Free Survival, safety, and tolerability. Exploratory outcome measures include Health-Related Quality of Life, Overall Survival, and biomarker assessments. All cohorts are open for enrollment. Cohort B has received collaborative support from the Society of Urologic Oncology-Clinical Trials Consortium (SUO-CTC). Clinical trial information: NCT06567743. Research Sponsor: CG Oncology.

TPS4626 **Poster Session**

Sasanlimab as bladder-sparing maintenance treatment after neoadjuvant chemotherapy in patients with muscle invasive bladder cancer (MIBC): The phase 2, SASAN-SPARING trial.

Elena Sevillano, Julia Martinez Perez, Nuria Lainez Milagro, Pablo Gajate Borau, Xavier Garcia del Muro, Javier Puente, Miguel Angel Climent, Alfonso Gomez de Liaño, Oscar Reig Torras, Guillermo de Velasco; HM CIOCC MADRID (Centro Integral Oncológico Clara Campal), Laboratorio de Innovación en Oncología, Instituto de Investigación Sanitaria HM Hospitales, Madrid, Spain; Department of Medical Oncology, Hospital Universitario Virgen del Rocío, Seville, Spain; Hospital Universitario de Navarra, Pamplona, Spain; Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; Medical Oncology Department, Institut Català d'Oncologia IDIBELL Research Institute, University of Barcelona, Barcelona, Spain; Hospital Clínico San Carlos, Madrid, Spain; Fundación Instituto Valenciano de Oncologia (IVO), Valencia, Spain; Department of Medical Oncology, Hospital Complex Insular-Materno Infantil, Las Palmas, Spain; Hospital Clinic de Barcelona; Translational Genomics and Targeted Therapeutics in Solid Tumors Lab, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; Hospital 12 de Octubre, Madrid, Spain

Background: Radical cystectomy (RC), traditionally considered the gold standard for MIBC, carries significant morbidity, negatively impacting patients' quality of life. Recent studies have demonstrated that neoadjuvant cisplatin-based chemotherapy combined with immunotherapy can induce a complete or major pathological response in a subset of patients, allowing consideration of less invasive therapeutic alternatives. High comorbidity rates in MIBC often preclude radical cystectomy. Sasanlimab, a PD-1 inhibitor, may enhance the efficacy of neoadjuvant chemotherapy, potentially enabling bladder preservation in responding patients and improving outcomes. **Methods:** The SASAN-SPARING trial is a single-arm, non-randomized, non-blinded, phase 2 trial that evaluates the efficacy and safety of sasanlimab as a maintenance treatment in patients with localized MIBC that undergo a bladder sparing strategy with neoadjuvant cisplatin-based chemotherapy. A total of 70 patients will be accrued in 10 hospitals of Spain. Patients are $\geq$ 18 years, ECOG 0-1 and treatment-naïve for MIBC candidates to receive neoadjuvant cisplatin/gemcitabine followed by RC. All patients receive 4 cycles of neoadjuvant chemotherapy with cisplatin (70 mg/m2) on day 1 every 3 weeks and gemcitabine (1000 mg/m2) on days 1 and 8 of a 3-week cycle. After neoadjuvant chemotherapy, patients are restaged and those achieving a clinical response (absence of disease by cytology, imaging, and cT0/Ta/T1/Tis) are allowed to proceed without RC and receive maintenance with sasanlimab 300 mg subcutaneous every 4 weeks for up to 12 cycles. Tumor assessments including MRI, cystoscopy and cytology are scheduled every 12 weeks. The primary endpoint is the bladder-intact overall survival (biOS) rate at 12 months after the first dose of sasanlimab. Assuming a 12-month biOS of 81% (H0) and an increase with sasanlimab up to 93% (H1), the study requires 70 patients included of which 47 are treated with sasanlimab (one arm survival test; α = 0.05 β= 0.8). The study includes an ambitious biomarker substudy to evaluate the use of ctDNA in blood and urine samples for tumor assessment and molecular dynamics under therapeutic pressure. In addition, gut microbiome and tumor samples will be used for this end. Study of biomarkers will provide a useful tool to corroborate achievement of a clinical complete response, contributing to personalized treatments. The study is approved and started with recruitment of patients in December 2024. Clinical trial information: NCT06623162. Research Sponsor: Fundación de Investigación HM Hospitales supported by a grant (#87884561) from Pfizer.

TPS4627 **Poster Session**

Intravesical sacituzumab tirumotecan in participants with intermediate-risk non–muscle-invasive bladder cancer: The phase 1/2 TroFuse-027 study.

Joshua J. Meeks, Roger Li, Ashish M. Kamat, Girish S. Kulkarni, Noah M. Hahn, Ekta Kapadia, Qing Zhao, Hema Kishore Dave, Max Kates; Northwestern University Feinberg School of Medicine, Chicago, IL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; University Health Network, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; The Johns Hopkins University School of Medicine, Baltimore, MD; Merck & Co., Inc., Rahway, NJ

Background: Standard treatment for patients with intermediate-risk (IR) non–muscle-invasive bladder cancer (NMIBC) is transurethral resection of bladder tumor (TURBT) with or without adjuvant intravesical chemotherapy or bacillus Calmette-Guérin. However, 30% to 50% of patients experience disease recurrence, which leads to repeated endoscopic resections and intravesical therapies that contribute to patient morbidity and decreased urinary quality of life. Therefore, novel therapies with favorable efficacy and safety profiles are needed. Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein expressed broadly in several tumors, including all stages of bladder cancer, making it a viable therapeutic target. Sacituzumab tirumotecan (sac-TMT; MK-2870) is an antibody-drug conjugate consisting of a humanized anti-TROP2 monoclonal antibody, a linker, and a cytotoxic belotecan-derivative topoisomerase I inhibitor. In *in vivo* mouse models, intravesical sac-TMT demonstrated antitumor activity, tolerability, and minimal systemic exposure. TroFuse-027 (NCT06637423) is a nonrandomized, open-label, phase 1/2 study designed to evaluate the safety and efficacy of intravesical sac-TMT as ablative therapy in participants with IR NMIBC.
Methods: Eligible participants are adults with prior history of pathologically confirmed low-grade Ta diagnosed with recurrence by visual inspection on cystoscopy who have not yet undergone TURBT and have urine cytology negative for high-grade urothelial carcinoma. In the phase 1 dose-escalation part, approximately 32 participants will be sequentially enrolled into 4 escalating sac-TMT dose groups using the Bayesian optimal interval design with a target dose-limiting toxicity rate of 30%; 3 to 14 participants are planned for each dose group. Sac-TMT will be administered by intravesical instillation weekly for 6 weeks unless there is unacceptable toxicity or withdrawal of consent. Disease assessments (per local urine cytology, cystoscopy, and biopsy as indicated for visible tumors) will occur at week 12 in all participants, then every 12 weeks for the first year and every 24 weeks thereafter for up to 2 years unless progression to high-grade NMIBC or muscle-invasive bladder cancer occurs. Participants with low-grade Ta that persists at week 12 or recurs anytime after that will undergo TURBT and remain in efficacy follow-up. The primary objectives are to evaluate safety and tolerability and to establish the recommended phase 2 dose. Secondary objectives are pharmacokinetics and complete response rate (the proportion of participants with the absence of visible tumors at the 12-week assessment after initiating treatment) and duration of complete response per local assessment. Future studies (phase 2) will be initiated on completion of dose escalation and based on the totality of data. Clinical trial information: NCT06637423. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4628 Poster Session

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

Guillermo de Velasco, Andrea Necchi, Yohann Loriot, Syed A. Hussain; Hospital 12 de Octubre, Madrid, Spain; IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; Gustave Roussy, Département de Médecine Oncologique et Département des Essais Précoces, Université Paris-Saclay, Villejuif, France; University of Sheffield, Sheffield, United Kingdom

Background: The standard treatment for nonmetastatic MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC). However, many patients are ineligible for cisplatin-based therapy. Immune checkpoint inhibitors (ICIs) have transformed the treatment of metastatic urothelial cancer (mUC), particularly for cisplatin-ineligible patients. Emerging evidence suggests that ICIs may also have potential as neoadjuvant therapy in resectable urothelial cancer, with preliminary data showing antitumor activity. Erdafitinib (ERDA), an FGFR inhibitor, has demonstrated efficacy in advanced urothelial cancer with FGFR2/3 mutations or fusions. In the phase 2 NORSE trial, ERDA combined with CET showed clinically meaningful activity in newly diagnosed FGFR-altered mUC. This study evaluates whether ERDA ± CET improves the pathological complete response (pCR) rate in FGFR-positive MIBC patients eligible for RC but ineligible for or declining cisplatin-based neoadjuvant therapy. **Methods:** SOGUG-NEOWIN is a prospective, non-comparative, open-label, multicenter trial assessing 9 or 12 weeks of neoadjuvant ERDA (cohort 1) or ERDA + CET (cohort 2) in patients with MIBC (cT2–T4a N0/1 M0) and FGFR alterations. Eligibility criteria include ECOG PS 0–1; predominant urothelial carcinoma histology; cisplatin ineligibility (GFR $<$ 60 mL/min, ≥grade 2 hearing loss, or ≥grade 2 neuropathy) or refusal; fitness for RC; no prior FGFR-targeted or anti-PD-(L)1 therapy, systemic therapy, or surgery (except TURBT or biopsies); prior BCG therapy allowed if completed ≥6 weeks before study treatment; and no current retinopathy. A total of 45 patients per cohort will be centrally allocated. Co-primary endpoints are pCR rate and pathological downstaging response ($<$ ypT2). Secondary endpoints include event-free survival, overall survival, response rate, safety, tolerability, and delay to surgery. Exploratory endpoints include biomarkers of response and resistance (baseline tissues, blood, urine), quality of life (FACT-Bl, EQ-5D-5L), and PET-MRI tumor response in a subset of patients. This trial is approved in 4 countries (6 sites in Spain, 3 in Italy, 5 in the UK, 5 in France) and is the first to systematically evaluate ERDA ± CET in FGFR-positive MIBC. The first patient was pre-screened on January 31, 2024. As of January 21, 2025, 68 patients were pre-screened, 6 were FGFR2/3-positive, and 4 were enrolled. (EU CT Number 2024-512573-27-01). Clinical trial information: 2024-512573-27-01. Research Sponsor: Johnson & Johnson.

TPS4629 Poster Session

The uTRACT registry: A single-arm, multicenter, prospective, and retrospective registry study to evaluate the real-world use of UGN-101 in participants with upper tract urothelial carcinoma (UTUC) in the United States.

Adam Feldman, Yair Lotan, Soloman Woldu, Mehrad Adibi, Marc Bjurlin, Eliza DeFroda, Rian J. Dickstein, Khurshid R. Ghani, David Hoenig, Joseph M. Jacob, Hristos Z. Kaimakliotis, Jennifer Linehan, Joshua J. Meeks, Katie S. Murray, Nirmish Singla, Karthik Tanneru, Hetal Pandya, Nikky Ugwuoke, Brent Burger, Michael J Louie, uTRACT Registry Study Group; Massachusetts General Hospital, Boston, MA; Department of Urology, UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Missouri, Columbia, MO; Chesapeake Urology, Hanover, MD; University of Michigan, Ann Arbor, MI; Northwell Health, Great Neck, NY; Department of Urology, Upstate Medical University, Syracuse, NY; Indiana University School of Medicine, Indianapolis, IN; Providence Specialty Medical Group, Santa Monica, CA; Northwestern University Feinberg School of Medicine, Chicago, IL; NYU Langone Health, New York, NY; Johns Hopkins Brady Urological Institute, Baltimore, MD; MUSC Health, Florence, SC; UroGen Pharma, Princeton, NJ

Background: Upper tract urothelial carcinoma (UTUC) constitutes 5–10% of primary urothelial carcinomas, affecting two in 100,000 people in the US annually. Peak incidence occurs in patients 70–90 years of age.[1–3] Low-Grade (LG) UTUC represents 40% of the total disease burden.[3] Endoscopically-guided ablation is often used to treat LG-UTUC, however recurrence is common, and the long-term surveillance risks potential complications in this elderly patient population. UGN-101 is a reverse thermal hydrogel formulation of mitomycin approved for chemoablative treatment of LG-UTUC, administered as a liquid in a chilled state, which converts to a gel depot at body temperature, resulting in a dwell time of 4–6 hours. In the phase 3 OLYMPUS trial, 42 of the 71 LG-UTUC patients treated with UGN-101 achieved complete response (CR) at 3 months.[4] Among the 41 patients followed after CR, median follow-up was 28.1 months (95% CI, 13.1-57.5), and median duration of response (DoR) was 47.8 months (95% CI, 13.0-not estimable).[5] **Methods:** The uTRACT registry (NCT05874921) is evaluating real-world data from patients administered UGN-101, post-FDA approval(15 Apr 2020). Approximately 400 patients >18 years old with UTUC who received ≥1 dose of UGN-101 will be enrolled at ~20 sites. Retrospective data will be collected from patients that received UGN-101 after approval as well as prospective data from newly eligible patients. UGN-101 is administered as 6 once weekly pyelocalyceal instillations retrograde via ureteral catheter or antegrade via a nephrostomy tube. Instillation volume is based on volumetric measurements, not to exceed 15 mL (60 mg of mitomycin). For participants with a CR 3 months after the first dose, once monthly maintenance instillations may be administered (up to 11 additional doses). Participant history and disease status are collected at baseline (prior to UGN-101 dosing), and dosing information, surveillance endoscopy and imaging results will be captured over a period of 3 years post baseline, at approximately 3, 6, 12, 24, and 36 months after the first instillation. Assessment of response will be based on endoscopic surveillance, imaging, cytology, and/or for-cause biopsy. Data analysis will be performed on the overall cohort (~400 participants) and the LG-UTUC cohort (expected to be ~340 participants). Outcomes collected include no evidence of disease at 3-months, DoR, recurrence free survival, time to recurrence/ progression and adverse events. The uTRACT registry started enrollment in 2023 with 228 patients recruited to date. 1. Siegel RL, et al. CA Cancer J Clin. 2022;72:7-33. 2. Rouprêt M, et al. Eur Urol. 2023;84:49-64. 3. Raman J, Shore ND. Rev Urol. 2020;22:1-8. 4. Kleinmann N, et al. Lancet Oncol. 2020;21:776-785. 5. Pierorazio PM, et al. J Urol. 2024: 101097ju0000000000004331. Clinical trial information: NCT05874921. Research Sponsor: UroGen Pharma.

TPS4630 Poster Session

ABLE-22: Safety and efficacy evaluation of nadofaragene firadenovec alone or in combination with chemotherapy or immunotherapy—A randomized, open-label, phase 2 study.

Siamak Daneshmand, Stephen A. Boorjian, Joshua J. Meeks, Trinity Bivalacqua, Yair Lotan, Wassim Kassouf, Girish S. Kulkarni, Paolo Gontero, Peter Albers, Joern Skibsted Jakobsen, Kristian Juul; Keck School of Medicine of USC, Los Angeles, CA; Mayo Clinic Rochester, Rochester, MN; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Urology, Hospitals of the University of Pennsylvania, Philadelphia, PA; UT Southwestern Medical Center, Dallas, TX; McGill University Health Centre, Montréal, QC, Canada; Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada; Dipartimento di Discipline Medico Chirurgiche, Clinica Urologica, University of Torino, Torino, Italy; Department of Urology, Heinrich-Heine-University, Düsseldorf, Germany; Ferring Pharmaceuticals A/S, Copenhagen, Denmark

Background: Bacillus Calmette-Guérin (BCG) is the standard first-line therapy for patients with high-risk non–muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) ± papillary tumors; however, patients whose disease is unresponsive to BCG therapy are unlikely to benefit from further courses of BCG. Bladder-preserving treatment options for patients with BCG-unresponsive NMIBC with CIS ± Ta/T1 include intravesical gene therapy (nadofaragene firadenovec-vncg), intravesical chemotherapy (gemcitabine and docetaxel), and immunotherapy (intravenous pembrolizumab and intravesical nogapendekin alfa inbakicept-pmln). In a pivotal phase 3 study, 53.4% of participants (55/103) with BCG-unresponsive NMIBC with CIS ± Ta/T1 achieved a complete response (CR) within 3 months of a single instillation of nadofaragene firadenovec, and of them, 45.5% (25/55) maintained a CR at 12 months. Nadofaragene firadenovec in combination with chemotherapy or immunotherapy may further improve clinical efficacy. ABLE-22 (NCT06545955) is an interventional study evaluating the safety and efficacy of nadofaragene firadenovec alone or in combination with chemotherapy (gemcitabine and docetaxel) or immunotherapy (pembrolizumab) in participants with high-risk BCG-unresponsive NMIBC. Participants not responding at month 3 will be offered reinduction.
Methods: ABLE-22 will include approximately 40 to 75 sites across the United States and Canada; sites in Asia, Australia, and Europe may be included. Participants (anticipated N = 150) will be randomly assigned 1:1:1 to receive nadofaragene firadenovec (n = 50), nadofaragene firadenovec plus gemcitabine and docetaxel (n = 50), or nadofaragene firadenovec plus pembrolizumab (n = 50). Adults aged ≥18 years with documented NMIBC with CIS ± Ta/T1 that is unresponsive to ≥2 courses of BCG therapy within the last 12 months are eligible to enroll. The primary endpoint is CR (defined as absence of low- and high-grade NMIBC) at months 3 or 6, as participants with persistent NMIBC (any CIS, low-grade Ta, and > 3 cm or multifocal high-grade Ta) will be offered reinduction once, at month 3. Secondary endpoints include durability of CR, incidence of muscle-invasive progression, cystectomy-free survival, pathologic staging, overall survival, and safety. Durability of CR will be followed up to month 36 (assessed quarterly for the first 24 months); all other secondary endpoints will be assessed up to and including month 36. Exploratory endpoints include changes in expression of potential biomarkers in blood and urine. Results from this investigational, randomized, multicenter, open-label study evaluating the safety and efficacy of nadofaragene firadenovec alone or in combination with chemotherapy or immunotherapy are expected July 2028. Clinical trial information: NCT06545955. Research Sponsor: Ferring Pharmaceuticals, Inc.

TPS4631 **Poster Session**

LEGEND: A phase 1/2 study of detalimogene voraplasmid (EG-70), an intravesical monotherapy for patients with high-risk non–muscle-invasive bladder cancer (NMIBC).

Jen-Jane Liu, Raj Satkunasivam, Rian J. Dickstein, Shreyas Joshi, Sam S. Chang, Gautam Jayram, Neal D. Shore, Yair Lotan, Anne K. Schuckman, Raj Pruthi, Anthony Cheung, Katherine Hubert Chan, Christine Tosone, Scott Johnson, Vignesh Packiam, Christine Ibilibor, Wassim Kassouf, Ashish M. Kamat, John Arthur Taylor III, Gary D. Steinberg; Oregon Health & Science University, Portland, OR; Houston Methodist-Weill-Cornell Medical College, Houston, TX; University of Maryland, Baltimore, MD; Emory University School of Medicine, Atlanta, GA; Vanderbilt University Medical Center, Nashville, TN; Urology Associates, Nashville, TN; Carolina Urologic Research Center, Myrtle Beach, SC; UT Southwestern Medical Center, Dallas, TX; University of Southern California, Los Angeles, CA; enGene Inc., Waltham, MA; enGene, Inc., Waltham, MA; Engene Usa, Inc., Waltham, MA; EnGene Inc., Waltham, MA; Medical College of Wisconsin, Milwaukee, WI; Rutgers Cancer Institute and Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; University of Virginia, Charlottesville, VA; McGill University Health Centre, Montréal, QC, Canada; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Kansas Medical Center, Kansas City, KS; RUSH University Medical College, Chicago, IL

Background: High-risk NMIBC is generally treated with adjuvant intravesical Bacille Calmette-Guérin (BCG). However, ~50% of patients experience recurrence and/or progression afterwards and are considered unresponsive. Detalimogene voraplasmid (EG-70) is an investigational, non-viral, non-integrating, intravesically administered gene therapy designed to elicit local stimulation of anti-tumor immune responses in the bladder and drive durable efficacy in NMIBC, while mitigating the risk of systemic toxicities from immune stimulation. The Phase 1 (dose-escalation) portion of the first-in-human Phase 1/2, open-label, multicenter study (LEGEND; NCT04752722) of detalimogene voraplasmid is complete. The Phase 2 dose was identified, treatment was generally well tolerated, with an overall complete response (CR) rate of 73% [Kalota S, et al. AUA 2024]. Herein, we describe the ongoing Phase 2 portion of the study, which opened to enrollment in May 2023, which recently added a new cohort of BCG-unresponsive HG Ta/T1 papillary only (no carcinoma *in situ* [CIS]) disease. **Methods:** Eligibility criteria: age ≥18 years; ECOG PS 0–2; NMIBC, with/without resected coexisting papillary tumors, ineligible for, or elected not to undergo, cystectomy; satisfactory bladder function. Patients receive detalimogene voraplasmid 0.8 mg/mL in 50 mL (intravesical administration, Weeks 1, 2, 5 & 6, 12-week cycle) for 4 cycles, and patients with CR at the end of the 4th cycle will enter maintenance treatment to receive 2 instillations per cycle (at Weeks 1 and 2) for up to another 8 cycles: BCG-unresponsive with CIS (Cohort 1); BCG-naïve with CIS (Cohort 2A) or BCG-exposed with CIS (Cohort 2B); BCG-unresponsive NMIBC with high-grade papillary disease without CIS (Cohort 3). Phase 2 primary endpoints: efficacy (CR rate at Week 48); safety. Secondary endpoints: progression-free survival; CR rate at Weeks 12, 24, 36, and 48; duration of response. The study is being conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with ICH/GCP. All patients provide written informed consent. The Phase 2 portion of the study is enrolling and will recruit approximately 300 patients across all cohorts, from sites in the USA, Canada, Europe, and the Asia-Pacific region. Clinical trial information: NCT04752722. Research Sponsor: enGene Inc.

TPS4632 Poster Session

ABLE-32: A randomized, controlled, phase 3b clinical trial of nadofaragene firadenovec-vncg versus observation in patients with intermediate-risk non–muscle-invasive bladder cancer.

Neal D. Shore, Mark Tyson, Gautum Agarwal, Evan R. Goldfischer, Michael Brandon Williams, Corine Baayen, Kristian Juul, Per Sandstrom, Vikram M. Narayan; Carolina Urologic Research Center, Myrtle Beach, SC; Mayo Clinic Arizona, Phoenix, AZ; Urologic Oncology and Precision Medicine, Mercy Oncology and Hematology—David C. Pratt Cancer Center, St. Louis, MO; Premier Medical Group of the Hudson Valley, Poughkeepsie, NY; Urology of Virginia, Eastern Virginia Medical School, Virginia Beach, VA; Ferring Pharmaceuticals A/S, Copenhagen, Denmark; Department of Urology, Emory University, Atlanta, GA

Background: There is currently no Food and Drug Administration (FDA)-approved treatment for intermediate-risk non–muscle-invasive bladder cancer (IR NMIBC), defined as recurrence of low-grade (LG) Ta within 1 year, solitary LG Ta > 3 cm, multifocal LG Ta, high-grade (HG) Ta (≤3 cm), and/or LG T1. Nadofaragene firadenovec-vncg is the first FDA-approved intravesical nonreplicating gene therapy for treating high-risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) ± papillary tumors. In a nonrandomized, multicenter, open-label, repeat-dose, phase 3 study, 53.4% of participants (55/103) with CIS ± HG Ta/T1 achieved complete response 3 months after the first instillation. Nadofaragene firadenovec was well tolerated, with no grade 4/5 study drug-related AEs. Because maintenance treatment with nadofaragene firadenovec following tumor resection may improve clinical outcomes in patients with IR NMIBC, the ABLE-32 open-label randomized study is being conducted to evaluate the efficacy of nadofaragene firadenovec administered every 3 months versus observation in participants with IR NMIBC. **Methods:** This phase 3 study includes approximately 100 global sites with 454 anticipated participants. Adults aged ≥18 years, diagnosed with new or recurrent IR NMIBC, and having undergone transurethral resection of bladder tumor within 60 days prior to randomization are eligible. Participants will be randomly assigned 1:1 to receive nadofaragene firadenovec or continue observation. The nadofaragene firadenovec group will receive quarterly doses unless disease recurs or progresses. The observation group will be followed quarterly and may receive nadofaragene firadenovec if IR NMIBC recurs within 24 months. All participants will be evaluated for recurrence and progression using cytology, cystoscopy, and for-cause biopsy for up to 5 years. The primary endpoint is recurrence-free survival (RFS), from randomization to first documented recurrence, progression, or death. Secondary endpoints include RFS at 12 and 24 months and safety. Exploratory endpoints include effect on potential biomarkers and health-related quality of life. Final results are expected in 2031. Clinical trial information: NCT06510374. Research Sponsor: Ferring Pharmaceuticals.