

A phase 2 randomized trial of radium-223 dichloride and cabozantinib in patients (pts) with renal cell carcinoma (RCC) with bone metastases (BM): RADICAL (Alliance A031801).

Rana R. McKay, Pamela J. Atherton, Karla V. Ballman, Heather Jacene, Ronald C. Chen, Atish Dipankar Choudhury, Joshua Michael Lang, Suzanne Cole, Tareq Al Baghdadi, Young Kwok, Alan Tan, Stephanie A. Berg, Himisha Beltran, Michael J. Morris, Bradley Alexander McGregor, Tian Zhang, Matthew D. Galsky, Jonathan E. Rosenberg, Daniel J. George, Toni K. Choueiri; UC San Diego Moores Cancer Center, San Diego, CA; Mayo Clinic Rochester, Rochester, MN; Dana-Farber Cancer Institute, Boston, MA; University of Kansas Medical Center, Kansas City, KS; University of Wisconsin, 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; Vanderbilt University Medical Center, Nashville, TN; Division of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Internal Medicine, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Mount Sinai Tisch Cancer Center, New York, NY; Duke Cancer Institute, Durham, NC

Background: BM occur in ~30% of RCC pts and are associated with poor survival and symptomatic skeletal events (SSEs). Radium-223, an alpha-emitting bone-seeking radioisotope, prolongs survival in advanced prostate cancer. A pilot study of radium-223 with VEGF tyrosine kinase inhibitors (TKI) in RCC with BM showed safety and early efficacy (McKay, CCR, 2018). Cabozantinib is a TKI that showed efficacy in BM. RADICAL (NCT04071223) was designed to investigate cabozantinib ± radium-223 in RCC with BM. **Methods:** This open label multicenter study enrolled RCC pts with ≥1 symptomatic BM not previously irradiated and Karnofsky performance status ≥60%. Prior therapies were allowed; non-clear cell population was limited to 20%. Randomization was 1:1 to cabozantinib with (Arm A) or without (Arm B) radium-223, stratified by osteoclast-targeted therapy (OTT), prior therapy, baseline opioid use, and IMDC risk. In Arm A, cabozantinib was 40 mg daily cycle 1, 60 mg thereafter if tolerated; radium-223 was 1.49 microcurie/kg IV every 28 days for 6 doses. In Arm B, cabozantinib was 60 mg daily. The primary endpoint was SSE-free survival (SSE-FS). Secondary endpoints were safety, objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). The study was designed with 85% power to detect improvement in 6-month SSE-FS from 65% to 78% (one-sided $\alpha=0.05$), with planned interim futility analysis at 50% of expected events. **Results:** From 12/2019 to 9/2025, 90 pts were enrolled and evaluable for the interim analysis. Median age was 63 years; 74.4% male, 90.0% White, 83.3% clear cell histology. 11.1% were treatment naïve, 80.0% received OTT, 51.1% had baseline opioid use. IMDC risk was 16.7% favorable, 68.9% intermediate, 14.4% poor. Median cabozantinib dose was 31.4 mg (Arm A) and 40.0 mg (Arm B); median radium-223 cycles was 6. Median follow-up was 13.1 (range 0.1–49.4) months with 50 events, 17 SSEs (Arm A: 10; Arm B: 7) and 33 deaths (Arm A: 13; Arm B: 20). Outcomes are in Table. 71 pts were evaluable for response. ORR was 22.2% (Arm A), 22.9% (Arm B). Any grade treatment-related adverse events were 97.7% (Arm A), 93.2% (Arm B); grade ≥3 were 65.9% (Arm A), 56.8% (Arm B). The trial closed after interim analysis as SSE-FS did not meet the prespecified futility boundary ($HR \leq 1$). **Conclusions:** Radium-223 did not improve the primary endpoint of SSE-FS when added to cabozantinib but a numerical prolongation in OS was observed. Combination treatment was safe. Alternative radiotherapeutics warrant investigation in RCC. Clinical trial information: NCT04071223. Research Sponsor: National Cancer Institute.

Interim efficacy analysis.

	Arm	Median (95% CI)	HR (95% CI)
Stratified SSE-FS	A	17.9 (15.0-NE)	1.24 (0.62-2.48)
	B	17.6 (10.9-NE)	
Unstratified SSE-FS	A	17.9 (15.0-NE)	0.90 (0.51-1.59)
	B	17.6 (10.9-NE)	
OS	A	32.2 (17.9-NE)	0.77 (0.42-1.41)
	B	21.3 (12.3-NE)	
Stratified PFS	A	11.0 (5.8-17.4)	1.39 (0.72-2.66)
	B	11.2 (9.0-18.5)	

A prospective, multi-center, phase Ib/II trial of first-line cadonilimab plus axitinib in advanced non-clear cell renal cell carcinoma.

Xu Hu, Xu Shi, Sike He, Junru Chen, Yuntian Chen, Qiyu Zhu, Junjie Zhao, Yifu Shi, Yanfeng Tang, Xingming Zhang, Jiayu Liang, Jinge Zhao, Jiyan Liu, Ni Chen, Pengfei Shen, Jin Yao, Guangxi Sun, Zhenhua Liu, Hao Zeng; Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; Department of Radiology, West China Hospital, Sichuan University, Chengdu, China; Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Department of Pathology, West China Hospital, Sichuan University, Chengdu, China

Background: Non-clear cell renal cell carcinoma (nccRCC) is a rare and heterogeneous disease with limited treatment evidence. Patients with nccRCC generally respond less favorably to systemic immunotherapy than those with clear cell RCC. However, current evidence for the treatment of nccRCC remains limited, underscoring the need for new strategies. Cadonilimab, a bispecific PD-1/CTLA-4 antibody, has shown antitumor activity in various solid tumors, but its efficacy in RCC remains unknown. Here, we report initial results from a phase Ib/II trial of cadonilimab plus axitinib in advanced nccRCC. **Methods:** This open-label, multi-center, single-arm, phase Ib/II trial included patients with metastatic or unresectable treatment-naïve nccRCC, regardless of PD-L1 status, to receive cadonilimab plus axitinib 5mg b.i.d. In phase I, a 3+3 dose-escalation design was adopted, starting at 10 mg/kg Q3W of cadonilimab with axitinib to evaluate safety. In phase II, an additional 31 patients were enrolled at the recommended phase II dose (RP2D). The primary endpoints were safety assessment in phase Ib and objective response rate (ORR) by RECIST v1.1 in phase II. **Results:** As of October 1, 2025, A total of 37 patients was enrolled (Phase Ib: n=6; Phase II: n=31), with a median follow-up duration of 14.4 months. In phase Ib, no DLTs were observed. AEs were reported in 100.0% (6/6) of cases. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 66.7% (4/6) of cases, including proteinuria, hypertriglyceridemia, myasthenia gravis, diarrhea and alanine aminotransferase increased. The RP2D for cadonilimab was 10 mg/kg. For secondary endpoints, ORR was 50% (2/4) and DCR was 100% (6/6). In phase II, the ORR was 51.6% (16/31). DCR was 96.8% (30/31). AEs were reported in 100.0% of cases. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 58.1% (18/31) of cases. All AEs were expected and manageable. The median PFS was 16.7 (95% CI, 11.8–NR). The median OS was NR at the data cutoff. For the total cohort, the median PFS was 17.3 (95% CI, 12.1–NR). The median OS was NR at the data cutoff. **Conclusions:** Cadonilimab combined with axitinib demonstrated encouraging efficacy and tolerability as first-line therapy in advanced nccRCC across subtypes in this multi-center phase Ib/II study. Clinical trial information: NCT05808608. Research Sponsor: None.

Summary of efficacy analysis and tumor response review per RECIST v1.1.			
	Phase Ib	Phase II	Total cohort
Objective response rate, n(%)	2 (50)	16 (51.6)	18 (51.4%)
Disease control rate, n(%)	6 (100)	30 (96.8)	36 (97.2%)
mPFS (95%CI) months	NR (17.3, NR)	16.7 (11.8–NR)	17.3 (12.1–NR)
mOS (95%CI) months	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)

ctDNA analysis in participants with renal cell carcinoma treated with adjuvant pembrolizumab or placebo in the KEYNOTE-564 trial.

Toni K. Choueiri, Piotr Tomczak, Naomi Balzer Haas, David F. McDermott, Balaji Venugopal, Se Hoon Park, Thomas Ferguson, Stefan N. Symeonides, Wayne Yen Hwa Chang, Jae Lyun Lee, Naveed Sarwar, Piotr Sawrycki, Chen-Hua Chuang, Yiwei Zhang, Razvan Cristescu, Cai Chen, Carol Elaine Pena, Rodolfo F. Perini, Joseph E. Burgents, Thomas Powles, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Poznan University of Medical Sciences, Poznan, Poland; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; Beth Israel Deaconess Medical Center, Boston, MA; Beatson West of Scotland Cancer Centre and University of Glasgow, Glasgow, United Kingdom; Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; Department of Medical Oncology, Fiona Stanley Hospital, Perth, Western Australia, Australia; Edinburgh ECMC, Edinburgh Cancer Centre and University of Edinburgh, Edinburgh, United Kingdom; Taipei Veterans General Hospital, Taipei, Taiwan; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Imperial College Healthcare NHS Trust, London, United Kingdom; Provincial Hospital in Torun, Torun, Poland; Merck & Co., Inc., Rahway, NJ; Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute, and Queen Mary University of London, London, United Kingdom

Background: In the phase 3 KEYNOTE-564 trial (NCT03142334), adjuvant pembrolizumab (pembro) was superior to placebo (pbo) in participants (pts) with clear cell renal cell carcinoma (ccRCC) at increased risk of recurrence post nephrectomy. We report an analysis of pretreatment and on-treatment ctDNA (using 2 versions of a ctDNA assay with different sensitivities) with clinical outcomes in KEYNOTE-564. **Methods:** Pts with ccRCC at increased risk of recurrence post nephrectomy were randomized 1:1 to pembro or pbo. ctDNA was evaluated using Natera's Signatera RUO tissue-exome-based 16-plex and 64-plex ctDNA assays. Primary objectives of this analysis were to evaluate the association of baseline ctDNA status and ctDNA status change from baseline to cycle 5 day 1 (C5D1) with disease-free survival (DFS). Significance was prespecified at multiplicity-adjusted $\alpha = 0.05$. Sensitivity (percentage of ctDNA-positive pts among all pts with a DFS event) and specificity (percentage of ctDNA-negative pts among all pts without a DFS event) to predict DFS were also evaluated. **Results:** 994 pts were randomized to pembro (n = 496) or pbo (n = 498). ctDNA samples from 736 pts (pembro n = 374; pbo n = 362) were analyzed at baseline and from 641 pts at C5D1 (pembro n = 314; pbo n = 327) using both assays. Median study follow-up was 69.5 mo (range 60.2–86.9). In both treatment arms, ctDNA was detectable at baseline in 40 pts (5.4%) using the 16-plex assay and 60 pts (8.2%) using the 64-plex assay. By risk group, using the 16-plex assay, ctDNA was detectable at baseline in 26 of 642 (4.0%) intermediate-high risk pts, 10 of 53 (18.9%) high-risk pts, and 4 of 38 (10.5%) M1 NED pts; using the 64-plex assay, ctDNA was detectable in 44 of 642 (6.9%) intermediate-high risk pts, 11 of 53 (20.8%) high-risk pts, and 5 of 38 (13.2%) M1 NED pts. For both assays, ctDNA positivity was negatively associated with DFS in both pembro and pbo arms (P 's < 0.05). ctDNA status at baseline showed low sensitivity and high specificity to predict DFS in both treatment arms (Table). Of pts with detectable ctDNA at baseline and evaluable ctDNA at C5D1, ctDNA clearance at C5D1 occurred in 6 of 10 pts in the pembro arm and 3 of 14 pts in the pbo arm using the 16-plex assay; and 10 of 18 pts in the pembro arm and 9 of 25 pts in the pbo arm using the 64-plex assay. In both assays, ctDNA change from baseline at C5D1 was associated with DFS for both pembro and pbo arms (P 's < 0.05). **Conclusions:** While sensitivity was low, ctDNA positivity was associated with worse DFS outcomes irrespective of the ctDNA assay used. ctDNA clearance was higher in the pembro arm than the pbo arm. These data highlight the limitations of these ctDNA assays in ccRCC. Clinical trial information: NCT03142334. Research Sponsor: Funding for this study was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

% (n/N)	Pembro Sensitivity	Pembro Specificity	Pbo Sensitivity	Pbo Specificity
Baseline ctDNA, 16-plex	12 (17/146)	98 (224/228)	10 (18/173)	99 (188/189)
Baseline ctDNA, 64-plex	15 (22/146)	96 (220/228)	15 (26/173)	98 (185/189)

Intravesical recombinant BCG combined with chemo-immunotherapy (chemo-IO) as perioperative therapy for patients with muscle-invasive bladder cancer (MIBC): Primary analysis of SAKK 06/19.

Richard Cathomas, Ulf Petrausch, Stefanie Hayoz, Lukas Bubendorf, Martin Spahn, Philipp Niederberger, Frank Stenner, Anita Hirschi, Ursula Vogl, Anja Lorch, Petros Tsantoulis, Stefanie Aepli, Andreas Erdmann, Raeto Strebel, Angela Fischer Maranta, Christian Daniel Fankhauser, Sabrina Chiquet, Sacha I. Rothschild, Cyrill Rentsch; Division of Oncology, Cantonal Hospital Graubünden, Chur, Switzerland; Division of Oncology/Hematology, Hirslanden Zurich, Zurich, Switzerland; Swiss Cancer Institute, Bern, Switzerland; University Hospital of Basel, Pathology, Basel, Switzerland; Lindenhof Spital, Bern, Switzerland; Luzerner Kantonsspital, Luzern, Switzerland; University Hospital Basel, Basel, Switzerland; Klinik Hirslanden Zurich, Zurich, Switzerland; Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale (EOC), Bellinzona, Switzerland; Universitätsspital Zürich, Zürich, Switzerland; Geneva University Hospitals, Geneva, Switzerland; Department of Oncology/Haematology, Cantonal Hospital St. Gallen, Switzerland, Sankt Gallen, Switzerland; Kantonsspital Baden, Baden, Switzerland; Kantonsspital Graubünden, Chur, Switzerland; Division of Oncology/Hematology, Kantonsspital Graubünden, Chur, Switzerland; Luzerner Kantonsspital, Zürich, Switzerland; Cantonal Hospital Baden, Center Oncology / Hematology, Department Internal Medicine, Baden, Switzerland and University of Basel, Basel, Switzerland; University of Basel, Basel, Switzerland

Background: Perioperative chemo-IO is a new standard for MIBC but pathological complete remission (pCR) rates remain modest. Intravesical Bacillus Calmette Guérin (BCG) is very effective in non-muscle invasive bladder cancer, inducing a local immune response and likely activation of adaptive immunity, with evidence of systemic immune modulation that may enhance downstream immune-oncological effects. The use of BCG in MIBC has not yet been explored, primarily due to concerns about systemic complications. The recombinant BCG vaccine VPM1002BC (rBCG) is associated with enhanced immunogenicity and an improved safety profile. We hypothesize that the combination of intravesical rBCG and chemo-IO in MIBC may act synergistically, augmenting systemic immune activation and hereby improve antitumor efficacy without compromising safety. **Methods:** SAKK 06/19 is an open-label single arm phase II trial for cT2–T4a N0–1 MIBC patients (pts) eligible for cisplatin and radical cystectomy with lymphadenectomy (RC). rBCG was instilled weekly x3 (day 1, 8, 15). Atezolizumab (Atezo) 1200 mg was administered on day 1 and then x4 every 3 weeks (q3w). Cisplatin and gemcitabine started on day 22 and were given for 4 cycles q3w followed by RC. Only in case of $\geq$ ypT2 or ypN+, Atezo q3w was given after surgery for 13 cycles. pCR defined as ypT0 ypN0 and assessed by central pathological review was the primary endpoint. Based on Simon's minimax 2-stage design with H0 pCR $\leq$ 35% and H1 pCR $\geq$ 55%, accrual of 46 pts was needed (including 15% dropouts). Secondary endpoints included event free survival (EFS), overall survival (OS), pathological response (PaR, $\leq$ ypT1N0), feasibility and safety. NCT04630730. **Results:** 47 pts were included between 04/22 and 04/25 at 10 Swiss sites. 7 pts did not undergo RC (6 refused, 1 unfit for surgery). Of the 40 resected pts 53% had cT2, 37% cT3, 10% cT4 and 88% cN0, 12% cN1. rBCG was instilled in 95% of pts, 78% had all 3 doses. 98% received 4 doses of Atezo and 95% had 4 cycles of platinum (20% switched to carboplatin). pCR according to central review was 65% (26/40; one-sided 95% CI lower boundary of 51%) and PaR was 80% (32/40). Overall pCR for all included pts was 55% (26/47). TRAEs overall, G3, G4 were 48%, 9%, 0% to rBCG, 55%, 15%, 2% to Atezo and 98%, 38%, 17% to chemotherapy. No treatment-related deaths occurred. At a median follow-up of 11.8 months 1-year overall EFS was 88% (95% CI 71 – 95) and OS 95% (95% CI 81 – 99). **Conclusions:** This is the first trial to combine intravesical rBCG with chemo-IO in MIBC. The combination was feasible and safe without unexpected toxicities. The centrally assessed pCR rate of 65% and PaR of 80% are among the highest reported in an unselected MIBC population. Integration of intravesical rBCG into novel MIBC treatment regimens appears highly promising, particularly in the context of bladder-preservation approaches. Clinical trial information: NCT04630730. Research Sponsor: Roche; Swiss State Secretariat for Education, Research and Innovation (SERI).

Feasibility and safety results from RAD-IO: A multi-stage trial of durvalumab with chemoradiotherapy with 5-fluorouracil and mitomycin C in patients with muscle-invasive bladder cancer.

Nicholas David James, Joseph van de Wiel, Maria De Santis, Omar Sadeeq Din, Daniel Ford, Shaista Hafeez, Robert A. Huddart, Ana Hughes, James Iddenden, Romaana Mir, Catalina Vassallo - Bonner, Anjali Zarkar, Sarah Pirrie, Syed A. Hussain; The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; University of Birmingham, Birmingham, United Kingdom; Department of Urology, Charité Universitätsmedizin Berlin, Berlin, Germany and Department of Urology, Medical University of Vienna, Vienna, Austria; Weston Park Cancer Centre, Sheffield, United Kingdom; Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom; The Institute of Cancer Research, Division of Radiotherapy and Imaging and The Royal Marsden NHS Foundation Trust, Radiotherapy Department, London, United Kingdom; Section of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Clatterbridge Cancer Centre NHS Foundation Trust, Bebington, Wirral, United Kingdom; Mount Vernon Cancer Center, Northwood, United Kingdom; Patient Representative, Sutton, United Kingdom; Department of Oncology and Metabolism, Sheffield Teaching Hospital, Sheffield, United Kingdom

Background: Immune checkpoint inhibitors have a defined role peri-operatively and in the adjuvant setting when cystectomy is used as radical definitive treatment (Powles, T., *et al.* 2024, Galsky, M. D., *et al.* 2024). Their role when chemoradiation therapy (CRT) is used as definitive treatment remains to be established. RADIO is a multi-stage partially randomised trial comparing CRT (RT/5FU/mitomycin C) with durvalumab (CRT-D) given prior to, concurrently and 12 months following CRT in localized muscle-invasive bladder cancer. The trial is funded by AstraZeneca. **Methods:** Eligible patients had T2–T4aNo–N2Mo urothelial carcinoma of the bladder. Neoadjuvant chemotherapy was delivered as standard of care, where fit, prior to trial therapy. After randomised feasibility and safety criteria were met, the trial transitioned to a single-arm CRT-D design. Here we report the primary endpoint of 1-year disease-free survival rate (1yDFS) for all evaluable CRT-D participants, plus progression free survival (PFS), disease free survival (DFS), and overall survival (OS). DFS patients with disease present at 3-month imaging are categorised as having never been disease free. The design aimed to detect 1yDFS improvement, based on our previous trials, from 60% (CRT) to 75% (CRT-D) with 80% power and one-sided $\alpha=0.10$. **Results:** All data are preliminary. Between Oct 2020–Mar 2024, 55 participants (45 male; 10 female) with median age 70 (IQR 62–76) years of whom 40 (73%) had T2No, 8 (14%) had T3No and 7 (13%) had TxN1–2 were enrolled to receive CRT-D. 41 (74.5%) received neoadjuvant CT. Of the 54 participants who started treatment, all completed planned RT (55Gy/20Fr); 47 (87%) within the expected timeframe, 7 (13%) required an extension (2–6 days) (toxicity 3, patient choice 3, other 1). Toxicities extending RT: urinary tract infection, chest pain, and low platelets. At abstract submission, 48/55 were evaluable: 1yDFS 79% (38/18; 95% CI 66%, 88%). 12-month Kaplan–Meier estimates were: PFS 83% (95% CI 73%, 94%), DFS 72% (95% CI 61%, 85%), OS 96% (95% CI 91%, 100%). Safety: 35 SAEs; 17 unrelated SAEs, 12 SARs, 6 SUSARs. 10 SAEs were related to durvalumab, 3 were related to CT, and 5 were related to both durvalumab and CT. 3 SAEs led to discontinuation (5FU 2, durvalumab 1). 168 AESIs have been reported (most common: diarrhoea (19%), rash (12%), creatinine increased (8%)), and an additional 41 grade ≥ 3 AEs. **Conclusions:** Durvalumab combined with CRT demonstrated promising 1-year DFS and survival outcomes compared to our previously reported CRT outcomes (Hall, E., *et al.* 2022) with manageable safety profile. CRT-D is a safe treatment with a side effect profile in keeping with known side effects of CRT and durvalumab. Further investigation is warranted. Clinical trial information: 43698103. Research Sponsor: AstraZeneca UK Limited.

Perioperative SHR-A2102, a novel nectin-4–targeted antibody-drug conjugate, in combination with adebrelimab for patients (pts) with muscle-invasive bladder cancer: Results from a phase 2/3 study.

Dingwei Ye, Xiaolin Lu, Yijun Shen, Yiping Zhu, Shusuan Jiang, Lianhua Zhang, Danfeng Xu, Hui Chen, Yong Tang, Hecheng Li, Xuebing Han, Kai Yao, Yonghua Wang, Yong Yang, Wei Chen, Xiaojian Xu, Yanyan Lu, Ce Wang; Fudan University Shanghai Cancer Center, Shanghai, China; Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Urology, Hunan Cancer Hospital, Changsha, China; Department of Urology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Urology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Harbin Medical University Cancer Hospital, Harbin, China; Guangxi Medical University Cancer Hospital, Nanning, China; Department of Urology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Department of Urology, Shanxi Cancer Hospital, Taiyuan, 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, Guangdong, China; Department of Urology, The Affiliated Hospital of Qingdao University, Qingdao, China; Second Department of Urology, Yunnan Cancer Hospital, Kunming, China; The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; Clinical Research Department, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: Muscle-invasive bladder cancer (MIBC) is an aggressive disease, with substantial recurrence risk after radical cystectomy and pelvic lymph node dissection (RC + PLND) alone. SHR-A2102 is a nectin-4–targeted antibody-drug conjugate carrying topoisomerase I inhibitor payload. This phase 2/3 study (NCT06879145) evaluates the efficacy and safety of SHR-A2102 in combination with adebrelimab (an anti-PD-L1 antibody) as perioperative treatment for MIBC. Here, we report the preliminary results from the phase 2 study. **Methods:** In the multicenter phase 2 part, pts aged ≥ 18 years, ECOG PS 0–1, with pathologically and radiographically confirmed T2–4aN0Mo or T1–4aN1Mo MIBC, and scheduled for RC + PLND were enrolled. Pts received neoadjuvant treatment with 4 cycles of intravenous SHR-A2102 (8 mg/kg, day 1 Q3W) and adebrelimab (1200 mg, day 1 Q3W), followed by surgical resection and 5 additional cycles of adjuvant SHR-A2102 (8 mg/kg, day 1 Q3W) plus 13 additional cycles of adjuvant adebrelimab (1200 mg, day 1 Q3W). The primary endpoints are the recommended phase 3 dose (RP3D) and investigator-assessed pathological complete response (pCR, defined as pT0N0). **Results:** As of Nov 24, 2025, 37 pts were enrolled; 91.9% were male and the median age was 66 years (IQR 59–74). The ECOG PS was 0 in 24.3% of pts and 1 in 75.7%. Regarding disease stage, 29.7% were classified as T2N0, 51.4% as T3–4aN0, and 18.9% as T1–4aN1. Among 7 pts with target lesions, the neoadjuvant regimen achieved an objective response rate of 71.4% (5/7; 95% CI 29.0–96.3) and a disease control rate of 100.0% (95% CI 59.0–100.0). A total of 27 pts underwent RC + PLND, 13 (48.1%, 95% CI 28.7–68.1) achieved pCR and 16 (59.3%, 95% CI 38.8–77.6) attained pathological downstaging ($< pT2N0$). Consistent pCR benefits were observed across all predefined subgroups, with creatinine clearance < 60 mL/min showing no discernible effect on pCR rates. Of the 10 pts who refused or were ineligible for radical surgery after neoadjuvant therapy, 5 received transurethral resection of bladder tumor and 3 of whom achieved a complete clinical response (cCR, defined as T0N0Mo). With the median follow-up of 4.7 months (IQR 2.1–6.6), 3 event-free survival events were reported. Grade 3 or higher adverse events occurred in 40.5% (15/37) of the pts, primarily decreased neutrophil count (16.2%) and decreased lymphocyte count (10.8%). No patient was ineligible for surgery due to adverse events. **Conclusions:** Perioperative treatment with SHR-A2102 plus adebrelimab showed promising efficacy and was well tolerated in pts with MIBC. This combination holds potential benefit even for pts with renal impairment, suggesting its clinical applicability may extend beyond cisplatin-eligible populations. These results support further investigation for SHR-A2102 plus adebrelimab in this population. Clinical trial information: NCT06879145. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Enfortumab vedotin plus pembrolizumab (EV+P) vs chemotherapy for previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC): 3.5-year follow-up and response analyses from the phase 3 EV-302 study.

Thomas Powles, Michiel S. Van Der Heijden, Jens Bedke, Begoña P. Valderrama, Eiji Kikuchi, Matthew D. Galsky, Yohann Loriot, Gopa Iyer, Evan Y. Yu, Jeannie Hoffman-Censits, Nataliya Mar, Christof Vulsteke, Srikala S. Sridhar, Jose Pablo Maroto-Rey, Se Hoon Park, Blanca Homet Moreno, Jasmine Lichfield, Xuesong Yu, Heidi Wirtz, Shilpa Gupta; Barts Cancer Centre, Queen Mary University of London, London, United Kingdom; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Urology & Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; Hospital Universitario Virgen del Rocío, Sevilla, Spain; St. Marianna University School of Medicine, Kawasaki, Japan; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Université Paris-Saclay Gustave Roussy, Villejuif, France; Memorial Sloan Kettering Cancer Center, New York, NY; 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, Johns Hopkins Medical Center, Baltimore, MD; University of California Irvine, Irvine, CA; Integrated Cancer Center Ghent, AZ Maria Middelares and Center for Oncological Research (CORE), Antwerp University, Antwerp, Belgium; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Merck & Co., Inc., Rahway, NJ; Astellas Pharma Europe Ltd, Addlestone, United Kingdom; Pfizer Inc., Bothell, WA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: EV+P is the preferred standard of care for previously untreated la/mUC based on the EV-302/KEYNOTE-A39 trial (NCT04223856). We present updated data with 3.5 years of median follow-up, including exploratory subgroup analyses focusing on patients who achieved a complete response (CR) after an initial partial response (PR). **Methods:** Patients were randomized 1:1 to EV 1.25 mg/kg IV (days 1 and 8 of each 3-wk cycle) and P 200 mg IV (day 1) or gemcitabine + cisplatin/carboplatin, with treatment until disease progression, toxicity, or maximum number of cycles. Dual primary endpoints were progression-free survival by blinded independent central review and overall survival (OS); safety was a secondary endpoint. **Results:** With 42.8 months of median follow-up (data cutoff: October 6, 2025), OS benefit favoring EV+P (n=442) vs chemotherapy (chemo; n=444) was maintained (median OS, 33.6 vs 15.9 months; 42-month OS rate, 44.0% vs 24.6%; HR, 0.53 [95% CI, 0.45–0.63]), with no new safety signals. Of responding patients, 45.1% achieved a CR in the EV+P arm (n=295) and 32.8% in the chemo arm (n=195). Data cutoff was Aug 8, 2024. Among patients with confirmed CR in the EV+P arm, 66.2% achieved a PR initially, then converted from a PR to a CR with a median of 5 additional EV cycles (IQR, 3.0–8.0). In this subgroup, mOS was not estimable (NE), and >80% of patients were alive after 3.5 years. Longer treatment duration did not lead to new safety concerns. Overall, the most common first subsequent treatment was platinum-based chemo in the EV+P arm (n=135 [30.5%]) and a PD-L1 inhibitor in the chemo arm (n=265 [59.7%]). In the EV+P arm, investigator-assessed responses to subsequent platinum chemo occurred in 28 of 135 evaluable patients (20.7%). **Conclusions:** EV-302 represents the longest follow-up available for EV+P in a phase 3 trial. After 3.5 years of median follow-up, EV+P continues to demonstrate superior efficacy vs chemo, with no new safety signals. Two-thirds of patients achieving CR converted from an initial PR, suggesting that treatment duration is relevant in maximizing outcomes. Clinical trial information: EV-302 NCT04223856. Research Sponsor: Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	EV+P All CR (n=133)	EV+P CR after PR (n=88)
Median OS (95% CI), months	NE (NE-NE)	NE (NE-NE)
42-month OS rate (95% CI), %	83.6 (75.6-89.1)	82.4 (71.8-89.43)
Median time to CR (IQR), months	4.3 (2.2-8.4)	6.6 (4.3-12.1)
Time to PR	—	2.1 (1.9-2.2)
Time from PR to CR	—	4.5 (2.2-10.1)
Median EV cycles prior to CR (IQR), n	6.0 (3.0-9.0)	8.0 (6.0-11.5)
EV cycles prior to PR	—	3.0 (3.0-3.0)
EV cycles from PR to CR	—	5.0 (3.0-8.0)
Median P cycles prior to CR (IQR), n	6.0 (3.0-10.0)	9.0 (6.0-12.0)
P cycles prior to PR	—	3.0 (3.0-3.0)
P cycles from PR to CR	—	6.0 (3.0-9.0)
Median total EV cycles (IQR), n	13.0 (8.0-28.0)	15.0 (9.0-30.0)
Median total P cycles (IQR), n	28.0 (10.0-35.0)	31.0 (12.5-35.0)

Initial results from NEXUS-01, a phase 1 study of LY4052031, an antibody-drug conjugate targeting Nectin-4, in participants with advanced or metastatic urothelial carcinoma.

Gopa Iyer, Xin Gao, Alexander Z. Wei, Inkeun Park, Kei Muro, Peter H. O'Donnell, Benjamin Garmez, Matthew D. Galsky, Anthony M. Joshua, Amita Patnaik, Nehal J. Lakhani, Alejandro Falcon Gonzalez, Daniel Castellano Gauna, Alexander Philipovski, Justin A. Call, Abhishek Tripathi, Amy E. Chang, Elizabeth A. Martin, Hongmei Han, Thomas Powles; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital, Harvard Medical School, Boston, MA; Department of Medicine, Columbia University Irving Medical Center, New York, NY; Asan Medical Center, Seoul, South Korea; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; University of Chicago, Chicago, IL; Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN; Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia; The START Center for Cancer Research, San Antonio, TX; The START Center for Cancer Research, Grand Rapids, MI; Hospital Universitario Virgen del Rocío, Seville, Spain; Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; Florida Cancer Specialists & Research Institute, Lake Mary, FL; The START Center for Cancer Research, Mountain Region, West Valley City, UT; Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; Eli Lilly and Company, Indianapolis, IN; St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom

Background: Enfortumab vedotin plus pembrolizumab (EVP) is the current first-line standard of care for locally advanced / metastatic urothelial carcinoma (mUC). However, subsequent treatment options are limited, representing an urgent and growing unmet need. Preclinical data suggest that EV resistance may be payload mediated and consequently Nectin-4 remains a viable target for alternative therapies. LY4052031 is a next generation anti-Nectin-4 ADC, comprising a humanized IgG1 antibody conjugated to Camp98, a novel topoisomerase I inhibitor, via a cleavable peptide linker with homogeneous drug antibody ratio of 8. Here, we report the initial clinical data from the phase 1 dose escalation cohort of NEXUS-01 (NCT06465069). **Methods:** Adults with locally advanced / mUC or other selected solid tumors were eligible. Participants (pts) must have received or were ineligible for available standard therapies, and have ECOG PS 0-1. Dose escalation utilized a Bayesian optimal interval design. Key endpoints were safety, PK, and antitumor activity of LY4052031 per RECIST v1.1. **Results:** As of 25 Nov 2025, 70 pts (47 mUC, 23 non-UC) received LY4052031 doses ranging from 0.6-5.4 mg/kg IV Q3W. Median age was 66 years (range, 31-82); 60% had ECOG PS 1. Among pts with mUC, 70% (33/47) had prior EV (6% [2/33] had discontinued EV due to treatment-related toxicity). LY4052031, total antibody, and Camp98 exhibited mostly linear, dose-proportional PK, except at 4.8-5.4 mg/kg for payload. The most common treatment-emergent AEs (TEAEs) were nausea (43%), alopecia (39%), fatigue (37%), decreased appetite (29%), constipation, diarrhea, dysgeusia, mucositis, vomiting (27% each), and anemia (24%). The most common grade ≥ 3 TEAE was anemia (13%). Low activity scores (AS) for CYP2D6, the metabolic clearance pathway for Camp98, were associated with increased dose-limiting toxicity at higher dose levels. Thus, the study was amended to require CYP2D6 genotyping prior to treatment with dedicated dose finding in pts with low AS (< 0.5). Response was assessed in efficacy evaluable pts, defined as all treated pts who had at least 1 post-baseline response assessment or who discontinued prior to the first post-baseline response assessment. In 21 efficacy evaluable mUC pts (AS ≥ 0.5) treated with 2.4-4.8 mg/kg, ORR was 48% (10/21) and DCR was 81% (17/21) with 1 CR, 9 PR, and 7 SD. Among those who had prior EV (8 EV and 7 EV/P), ORR was 40% (6/15) and DCR was 80% (12/15) with 1 CR, 5 PR, and 6 SD; in the EV naïve pts, ORR was 67% (4/6) and DCR was 83% (5/6) with 4 PR and 1 SD. Median follow-up was 7 months (95% CI, 2.79-NE); median DoR was 7 months (95% CI, 2.7-NE). **Conclusions:** LY4052031 demonstrated promising clinical activity at multiple dose levels, including in EV pre-treated mUC. CYP2D6 AS specific dose optimization is ongoing and updated results will be presented. Clinical trial information: NCT06465069. Research Sponsor: Eli Lilly and Company.

Health-related quality of life (HRQoL) with neoadjuvant and adjuvant (neoadj-adj) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin ineligible: Phase 3 KEYNOTE-905 study.

Peter H. O'Donnell, Nabil Adra, Nimira Alimohamed, Ja Hyeon Ku, Pongwut Danchaivijitr, Anders Ullén, Alejo Rodriguez-Vida, Maksym Sabadash, Gunhild Von Amsberg, Viktor Paramonov, Steffen Rausch, Jens Bedke, Neal D. Shore, Matthew D. Galsky, Jasmine Lichfield, Changting Meng, David Huang, Chethan Ramamurthy, Allison Martin Nguyen, Christof Vulsteke; University of Chicago, Chicago, IL; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; University of Calgary, Calgary, AB, Canada; Seoul National University Hospital, Seoul, South Korea; Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; Hospital del Mar, Barcelona, Spain; Lviv State Regional Oncological Center, Lviv, Ukraine; University Medical Center Hamburg-Eppendorf; Martini Clinic, Hamburg, Germany; Cherkassy Regional Oncology Center, Cherkassy, Ukraine; Eberhard Karls University Tübingen, Tübingen, Germany; Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; START Carolinas/Carolina Urologic Research Center, Myrtle Beach, SC; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Astellas Pharma Europe Ltd, Addlestone, United Kingdom; Pfizer, Bothell, WA; Merck & Co., Inc., Rahway, NJ; Integrated Cancer Center Ghent, AZ Maria Middelares Ghent, Belgium; and Center for Oncological Research (CORE); Antwerp University, Antwerp, Belgium

Background: In KEYNOTE-905/EV-303 (NCT03924895), neoadj-adj EV + pembro and radical cystectomy (RC) + pelvic lymph node dissection (PLND) showed significant and meaningful improvements in EFS, OS, and pathologic complete response vs RC + PLND in pts with MIBC who were ineligible for or declined cisplatin (cis) therapy. Prespecified exploratory HRQoL outcomes are reported. **Methods:** Pts with MIBC who were ineligible/declined cis were randomized 1:1 to neoadj-adj EV + pembro and RC + PLND or RC + PLND (control). HRQoL was analyzed in pts who completed ≥ 1 PRO assessment. EQ-5D-5L and Functional Assessment of Cancer Therapy (FACT)—Bladder-Cystectomy (Bl-Cys) with FACT-general (FACT-G) and Bladder Cancer Index (BCI) were assessed predose on D1 of neoadjuvant cycles 1 (baseline [BL]), 2, and 3; pre- and post-surgery; and predose on D1 of adjuvant cycles 1, 2, 4, 8, and 12 in the EV + pembro arm. In the control arm, assessments were at pre- (BL) and post-surgery. In both treatment (Tx) arms, assessments were also done at Tx discontinuation, Q12W for ≤ 2 y, and Q24W thereafter. End points included mean (95% CI) change from BL to post-surgery wk 18 in FACT-G score; FACT-Bl-Cys scores (Bl-Cys subscale and Trial Outcome Index [TOI]); BCI urinary, bowel, and sexual scores; and EQ-5D-5L visual analog scale (VAS). **Results:** At post-surgery wk 18, completion and compliance rates for all assessments were $\geq 65\%$ in the EV + pembro arm and $>86\%$ in the control arm. Mean changes from BL to post-surgery wk 18 were similar between arms for FACT-G total and FACT-Bl-Cys subscale scores; FACT-Bl-Cys TOI score; BCI urinary, bowel, and sexual scores; and EQ-5D-5L VAS score (Table). BCI sexual and bowel score diminution was observed in both arms. For all PRO assessments, mean changes from BL over time were similar between Tx. **Conclusions:** The addition of neoadj-adj EV + pembro did not decrease HRQoL 18 wk post-surgery relative to RC + PLND alone; BCI bowel and sexual domains worsened in both arms, consistent with prior reports of RC impact. Given the superior efficacy and manageable safety, these results support the benefit/risk profile of EV + pembro and RC + PLND as Tx for pts with MIBC ineligible for or declining cis. Clinical trial information: NCT03924895. Research Sponsor: The study was conducted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA in collaboration with Astellas Pharma Inc., Northbrook, IL, USA and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

Mean change from BL to post-surgery wk 18, (95% CI), n	EV + pembro	Control
FACT-G total score	-2.73 (-6.22 to 0.75) n = 102	-2.84 (-6.11 to 0.43) n = 75
FACT-Bl-Cys (subscale/symptom index) total score	1.31 (-0.70 to 3.32) n = 102	1.85 (-0.59 to 4.29) n = 75
FACT-Bl-Cys TOI	-1.89 (-5.61 to 1.84) n = 102	-0.58 (-4.35 to 3.20) n = 75
BCI urinary	-2.03 (-6.12 to 2.07) n = 101	-0.05 (-5.90 to 5.80) n = 70
BCI bowel	-4.75 (-8.73 to -0.77) n = 101	-4.27 (-7.93 to -0.61) n = 70
BCI sexual	-15.46 (-20.53 to -10.39) n = 94	-17.88 (-24.36 to -11.40) n = 61
EQ-5D-5L VAS	-2.52 (-7.23 to -2.19) n = 102	-0.39 (-5.14 to 4.36) n = 75

Durvalumab monotherapy versus active monitoring for resected primary renal cell carcinoma in RAMPART: An international, phase 3, randomized controlled trial.

James M.G. Larkin, Thomas Powles, Elena Frangou, Grant D. Stewart, Laurence Albiges, Ian D. Davis, Martin R. Stockler, Cristina Suárez, Balaji Venugopal, Paul D. Nathan, Axel Bex, Craig Gedye, David Harrison, Tim Eisen, Toni K. Choueiri, Grisma Patel, Sophie Merrick, Babak Choodari - Oskooei, Mahesh M.K. Parmar, Angela Mary Meade, RAMPART Trial Investigators and Trial Team; The Royal Marsden NHS Foundation Trust, London, United Kingdom; 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 College London, London, United Kingdom; University of Cambridge, Cambridge, United Kingdom; Department of Medical Oncology, Gustave Roussy, Paris Saclay University, Villejuif, France; Monash University and Eastern Health, Box Hill, Australia; The University of Sydney, Camperdown, Australia; Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, United Kingdom; Mount Vernon Hospital, Northwood, United Kingdom; Royal Free London NHS Foundation Trust, UCL Division of Surgery and Interventional Science, London, United Kingdom; Calvary Mater Newcastle, Waratah, Australia; School of Medicine, University of St Andrews, St Andrews, United Kingdom; Dana-Farber Cancer Institute, Boston, MA; UCL, London, United Kingdom; Medical Research Council Clinical Trials Unit at University College London, Institute of Clinical Trials & Methodology, London, United Kingdom; Medical Research Council Clinical Trials Unit at University College London, London, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

Decision regret and toxicity perception following adjuvant pembrolizumab in renal cell carcinoma.

Elizabeth Nally, Veda Kudva, Gina Sherpa, Yifan Wang, Federica Sordelli, Giuseppe Basile, Sara Coca Membribes, Catherine Graham, Francesca Jackson-Spence, Bernadett Emma Szabados, Naveed Sarwar, Axel Bex, Antonio Rullan, Thomas Powles; Barts Cancer Institute, London, United Kingdom; Royal Free Hospital, London, United Kingdom; Imperial College Healthcare NHS Trust, London, United Kingdom; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Royal Free London NHS Foundation Trust, UCL Division of Surgery and Interventional Science, London, United Kingdom; Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, United Kingdom

Background: Adjuvant pembrolizumab (pembro) is standard of care in renal cell carcinoma (RCC). We explored whether patients retrospectively regret their decision to receive adjuvant pembro and hypothesised that this is related to long-term toxicity that is not adequately captured by CTCAE criteria. To address this we developed a patient-informed tool, co-designed with patients, focusing specifically on long-term toxicity. **Methods:** Patients with RCC who received adjuvant pembro across three tertiary cancer centres in London between June 2022–Dec 2024 were invited to participate. Eligible patients completed the validated Ottawa Decision Regret Scale (DRS) and a complementary questionnaire exploring factors influencing regret including toxicity and disease recurrence. CTCAE-graded immune-related adverse events (irAEs) were collected and correlated with decision regret (DR). In parallel, patients categorised irAEs as life-changing, significant or non-significant and these were correlated with DR. DRS > 25 was defined as moderate-high regret. Appropriate ethical approval was obtained. **Results:** 104 patients were included post adjuvant pembro (88% pT3N0, 4% pT3N1 and 8% M1 NED). Median follow up was 30 months. 14% patients have relapsed. CTCAE $\geq$ G3 irAEs occurred in 18%. 28% and 11% reported toxicity as significant (S) or life changing (LC) respectively. Patient reported S and LC toxicity did not correlate with $\geq$ G3 CTCAE ($p=0.11$), with 33% CTCAE G1–2 events reported as significant. Mean DR score was 14.9 (95% CI 8.5–21.3) with 13% expressing regret. 1/14 patients who had disease recurrence expressed regret (mean DRS = 10.3 [1.4–19.3]). Patients that reported LC & S toxicity expressed more regret (26.9 LC v 26.1 S v 2.1 NS, $p=0.0021$). There was no difference in regret between patients that sustained CTCAE G1–2 versus G3–4 irAE (14.9 vs 15.1, $p=0.23$). DR was highest with permanent endocrine ($n=24$) or musculoskeletal ($n=22$) irAEs (endo: DRS 28.8 v 9.5, $p=0.003$; MSK: DRS 25.1 v 12.8, $p=0.042$). Lower baseline expectations of toxicity correlated with greater DR ($p=0.002$). **Conclusions:** DR after adjuvant pembro is driven by long-term, low-grade toxicity rather than disease recurrence. Novel patient-informed tools that capture life-changing or permanent toxicities outperform CTCAE in identifying patients at risk of regret. Improved baseline education on long-term risks may reduce decision regret and improve shared decision-making. Research Sponsor: None.

Health-related quality of life (HRQOL) with pembrolizumab or observation for high-risk muscle-invasive urothelial carcinoma after surgery: Results from the AM-BASSADOR randomized trial (Alliance A031501).

Ronald C. Chen, Amylou C. Dueck, Briant Fruth, Michael J. Morris, Stephanie A. Berg, Jonathan E. Rosenberg, Andrea B. Apolo; University of Kansas Medical Center, Kansas City, KS; Department of Quantitative Health Sciences, Mayo Clinic Arizona, Phoenix, AZ; Division of Biomedical Statistics and Informatics, Mayo Clinic Rochester, Rochester, MN; Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: The AMBASSADOR trial (NCT03244381) showed that in patients with high-risk muscle-invasive urothelial carcinoma after radical surgery, adjuvant pembrolizumab for one year improved disease-free survival from 14.2 to 29.6 months (Apolo et al, NEJM 2024). Here we report the HRQOL results. **Methods:** HRQOL was completed by 560 randomized patients and included the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 plus the bladder cancer supplement BLM30, and the EQ-5D-5L, which assesses overall quality of life or health state. Published minimally important difference thresholds for EQ-5D-5L is 0.06, and for EORTC instruments is 5-10 points. For all reported HRQOL data, higher score is better except BLM30 urinary symptoms, where higher score indicates more symptoms. **Results:** Mean changes from baseline to 12 months (corresponding to end of treatment) for each HRQOL measure are summarized in the Table. No statistically significant difference was seen between the observation vs. pembrolizumab arms. Further, numerical differences between arms for these HRQOL measures do not meet (are lower than) the published minimally clinically important difference thresholds. **Conclusions:** Adjuvant pembrolizumab after radical surgery for patients with high-risk muscle-invasive urothelial carcinoma improved disease-free survival without negatively affecting HRQOL. These HRQOL results add further support to adjuvant immune checkpoint blockade therapy in these patients. Support: U10CA180821, U10CA180882, UG1CA189823 (<https://acknowledgments.alliancefound.org>). Clinical trial information: NCT03244381. Research Sponsor: U.S. National Institutes of Health; U10CA180821, U10CA180882, UG1CA189823.

HRQOL mean change from baseline to 12 months and between-arm comparisons.

	A) Observation	B) Pembrolizumab	Difference A vs B	P-value
EQ-5D-5L Index Value	-.029	-.012	-.02	.45
QLQ-C30 Global Health	0.07	1.45	-1.38	.55
QLQ-C30 Physical Functioning	-.089	-.069	-0.02	.99
QLQ-C30 Role Functioning	3.22	-1.23	4.45	.15
BLM30 Urinary Symptoms	-3.44	-3.02	-.42	.87
BLM30 Sexual Functioning	-.53	4.15	-4.68	.07

MAIN-CAV: Phase III randomized trial of maintenance cabozantinib and avelumab versus avelumab after first-line platinum-based chemotherapy (PBC) in patients (pts) with locally advanced/metastatic urothelial cancer (la/mUC; Alliance A032001).

Shilpa Gupta, Karla V. Ballman, Andrea B. Apolo, Srikala S. Sridhar, Ronald C. Chen, Timothy An-thy Chan, Yujia Wen, Stephanie A. Berg, Aihua Edward Yen, Shiva Baghaie, Parminder Singh, Melissa A. Reimers, Michael J. Morris, Matthew D. Galsky, Jonathan E. Rosenberg; Department of Hematology and Oncology, Cleveland Clinic - Taussig Cancer Institute, Cleveland, OH; Mayo Clinic Rochester, Rochester, MN; National Cancer Institute, National Institutes of Health, Bethesda, MD; Princess Margaret Cancer Centre, Toronto, ON, Canada; University of Kansas Medical Center, Kansas City, KS; Cleveland Clinic Lerner Research Institute, Cleveland, OH; University of Chicago, Chicago, IL; Alliance Protocol Operations Office, Chicago, IL; Division of Hematology and Oncology, Baylor College of Medicine, Dan L. Duncan Comprehensive Cancer Center, Houston, TX; Mayo Clinic Arizona, Phoenix, AZ; Division of Oncology, Department of Internal Medicine, Washington University in St. Louis, St. Louis, MO; Memorial Sloan Kettering Cancer Center, New York, NY; Mount Sinai Tisch Cancer Center, New York, NY

Background: Maintenance avelumab is a standard of care in patients (pts) with la/mUC who do not progress after first-line PBC. Cabozantinib (CABO) is an oral inhibitor of MET, VEGFR and TAM, active in multiple solid tumors. We hypothesized that an avelumab (Av)-CABO combination would improve outcomes in pts with mUC with an acceptable safety profile compared to avelumab maintenance alone. **Methods:** MAIN-CAV (NCT05092958) is a phase III randomized, multicenter, international trial for la/mUC pts who did not progress after 4–6 cycles of any PBC (gemcitabine-cisplatin, gemcitabine-carboplatin, MVAC, ddMVAC). Pts were randomized 1:1 to Av 800 mg IV every 2 weeks alone or with CABO 40 mg daily for ≤ 2 years. Stratification factors were response to first-line PBC (complete response [CR] vs partial response [PR] vs stable disease [SD]) and visceral metastases. The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), safety and quality of life. The target accrual was 654 pts; the trial closed early after enrollment of 68 pts following adoption of enfortumab vedotin plus pembrolizumab as the new preferred first-line standard in the US. **Results:** From 3/2022 to 3/2024, 68 pts were randomized (Av n = 33; CABO-Av n = 35). Median OS was 24.8 months (mo) with Av and 23.0 mo with Avb-CABO (Hazard ratio 1.41; 95% CI 0.66–3.01; p = 0.186). Median PFS was 4.6 mo with Av vs 6.0 mo with Av-CABO (p = 0.343). Objective response rate among pts with PR or SD after first-line PBC was 20.8% with Av vs 11.5% with Av-CABO (p = 0.424). Grade ≥ 3 treatment-related adverse events occurred in 24.2% pts on the Av arm vs 39.4% of pts on the Av-CABO arm and CABO dose reductions occurred in 63% of pts. **Conclusions:** Addition of CABO to Av did not improve OS or PFS compared with Av alone in this underpowered, prematurely closed phase III trial; safety was consistent with known profiles. U10CA180821, U10CA180882; U24CA196171, U10CA180863. (CCTG); U10CA180888 (SWOG); <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT05092958. Research Sponsor: U10CA180821, U10CA180882; U24CA196171, U10CA180863 (CCTG); U10CA180888 (SWOG).

Phase II study of frontline gemcitabine, 5-fluorouracil/leucovorin, and cisplatin (GemFLP) in advanced urachal and non-urachal urinary tract adenocarcinoma.

Emanuele Crupi, Jianjun Gao, Paul Gettys Corn, Lance C. Pagliaro, Charles C. Guo, Bogdan Czerniak, Mohammad Jad Moussa, Zachariah Thomas, Cindy Y. Jiang, Omar Alhalabi, Matthew T. Campbell, Arlene O. Siefker-Radtke; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic Rochester, Rochester, MN; Department of Pathology, Division of Pathology and Laboratory Medicine, 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 GU Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Adenocarcinomas of the urinary tract are rare malignancies with limited prospective data. Outcomes of triplet chemotherapy remain poorly defined. **Methods:** This was a prospective, single-arm, phase II study (NCT00082706) conducted at MD Anderson. Between 2005 and 2010, patients (pts) aged ≥ 18 years with ECOG 0–2 and metastatic or unresectable urachal (UA) or non-urachal adenocarcinoma (NUA) received frontline GemFLP (5-fluorouracil 200 mg/m² continuous infusion $\times 5$ days with leucovorin 23 mg IV daily $\times 5$; cisplatin 20 mg/m² IV daily $\times 5$; gemcitabine 200 mg/m² IV on days 1 and 5). Best overall response (BOR) was assessed by imaging. Primary endpoints were objective response rate (ORR) and overall survival (OS); secondary endpoint was toxicity. PFS was calculated from treatment initiation and duration of response (DoR) from first CR/PR to progression or death; time-to-event endpoints were estimated by Kaplan–Meier (KM). Post hoc analyses evaluated baseline tumor markers (CEA, CA19–9, CA125, β -hCG). Treatment-related adverse events (TRAEs) were graded per CTCAE v5. **Results:** Forty-six pts were enrolled (28 UA, 18 NUA). Median age was 58 years; 41% were de novo metastatic, and 78% had visceral metastases. ORR was 44% (20/46). Among responders, median DoR was 8.6 months (95% CI 4.6–30.8). median PFS was 3.3 months (95% CI 2.3–8.4) and median OS (mOS) was 21.0 months (95% CI 15.9–35.3). There was no difference in PFS ($p=0.39$) or OS ($p=0.99$) between UA and NUA. Baseline CEA, CA19–9, CA125, and β -hCG were not associated with ORR or PFS. Higher baseline CA125 was associated with inferior OS (HR 1.33, 95% CI: 1.12–1.58; $p=0.001$). Subsequent systemic therapy was administered to 28 pts (60.9%); median number of subsequent treatment lines was 2 (range 1–5). The most common hematologic TRAEs were anemia (28.1%; grade ≥ 3 [G3] 12.5%), thrombocytopenia (21.9%; G3 12.5%), and neutropenia (12.5%; G3 9.4%). The most frequent non-hematologic TRAEs were dehydration (21.9%; G3: 6.2%), diarrhea (9.4%; G3 6.2%) and catheter-related thrombosis (9.4%; G3 9.4%). No grade 5 events occurred. **Conclusions:** In this prospective phase II study, frontline GemFLP achieved a 44% ORR with durable responses (mDoR 8.6 mo) and 21 mo mOS in advanced UA and NUA. Survival did not differ between UA and NUA subtypes. Baseline CA125 was associated with OS. Toxicity was manageable. These data provide a prospective benchmark for this rare disease. Clinical trial information: NCT00082706. Research Sponsor: None.

Variable	UA (n=28)	NUA (n=18)
Characteristics		
Age, median [ICR]	58 [54– 62]	67 [62-72]
Race, n (%)		
White	22 (79)	11 (61)
Black	6 (21)	6 (33)
Other	0	1 (6)
Prior surgery for localized disease, n (%)	18 (64)	5 (28)
Mets at baseline	24 (86)	7 (39)
Lung	6 (21)	4 (22)
Liver	3 (11)	0
Peritoneum	17 (61)	0
Bone	3 (11)	3 (17)
Nodal-only mets	1 (3)	2 (10)
Outcomes		
ORR (%)	43.5	55.6
BOR n (%)		
CR	4 (14)	2 (11)
PR	6 (21)	8 (44)
SD	11 (39)	4 (22)
PD	6 (21)	3 (17)
NE	1 (4)	1 (6)

Interim analysis results from Duravelo-2: Zelenectide pevedotin (zele; BT8009) + pembrolizumab in patients (pts) with previously untreated locally advanced/metastatic urothelial carcinoma (la/mUC).

Yohann Loriot, Daniel P. Petrylak, Cong Xu, Ananya De, Hongmei Xu, Michael Method, Leslie DeMars; University Paris-Saclay, Gustave Roussy, Villejuif, France; Yale School of Medicine, New Haven, CT; Bicycle Therapeutics, Cambridge, MA

Background: Zele is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4, a protein overexpressed in la/mUC. There remains an unmet need in la/mUC for safer and more tolerable treatments. Here, we report an interim analysis (IA) for zele + pembrolizumab (pembro) dosage selection from the Phase 2/3 Duravelo-2 study (NCT06225596/BT8009-230) in previously untreated (untx) pts with la/mUC. **Methods:** Adults with la/mUC were enrolled into 2 cohorts: previously untx pts eligible for platinum-based chemotherapy (Cohort [Co]1) or pts with ≥1 prior systemic therapy (Co2). IA was conducted to determine the optimized dosage of zele + pembro (Co1) or zele monotherapy (Co2). Herein, we report IA results from Co1. Pts in Co1 were randomized 1:1:1 to: zele 5 mg/m² on Days [D]1/8/15 + pembro 200 mg on D1; or zele 6 mg/m² on D1/8 + pembro 200 mg on D1; or gemcitabine + cisplatin/carboplatin ± avelumab on a 21-D cycle. Dosage optimization included safety, efficacy, and pharmacokinetic data in pharmacometric and utility score analyses to quantify benefit-risk. **Results:** IA was performed at 27 weeks of follow-up (N=30 each zele dose group). Median zele treatment (tx) duration was 6.21 months. Confirmed ORRs by BICR among randomized, dosed pts with measurable disease at baseline were 55% (16/29; 7 complete responses [CR], 9 partial responses [PR]; 95% CI 35.7–73.6) and 58% (15/26; 8 CR, 7 PR; 95% CI 36.9–76.6) with zele 5 mg/m² and 6 mg/m², respectively. Zele-related adverse events (AEs) were reported in 97% (47% Gr ≥3) of pts at 5 mg/m² and 90% (40% Gr ≥3) at 6 mg/m². Gr ≥3 zele-related AEs for 6 mg/m² (≥5% pts) included neutropenia (10%), neutrophil count decreased (7%), and anemia (7%). AEs related to pembro were reported in 80% (37% Gr ≥3) and 53% (13% Gr ≥3), respectively. Zele-related AEs of clinical interest (AECIs) for 6 mg/m² are summarized in the Table. Notably, no zele-related severe skin reactions of any Gr were reported at the 6 mg/m² dosage. Zele dose reductions and discontinuations due to zele-related AEs occurred in 20% and 3%, respectively, for 6 mg/m². At Week 27, >50% of pts remained on tx. **Conclusions:** Zele at 5 mg/m² on D1/8/15 + pembro and 6 mg/m² on D1/8 + pembro on a 21-D cycle demonstrate encouraging response rates and safety profiles with the potential to differentiate from ADCs in previously untx pts. The 6 mg/m² D1/8 regimen demonstrated a more favorable benefit-risk profile to meet the need for safer and more tolerable treatments, with substantially reduced toxicity, better tolerability, improved potential for combinability, and enhanced convenience, leading to fewer discontinuations. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

Zele-related AECIs in pts with previously untx la/mUC treated with zele 6 mg/m ² on D1/8 + pembro (N=30).		
AECI, n (%)	Any Grade	Grade ≥3
Peripheral neuropathy	11 (37)	1 (3)
Skin reactions	5 (17)	0
Eye disorders	3 (10)	0
Hyperglycemia	0	0

Initial results from EXCEED, a phase 1 study of LY4101174, an antibody-drug conjugate targeting Nectin-4, in participants with advanced or metastatic urothelial carcinoma.

Xin Gao, Rafael Morales-Barrera, Tian Zhang, Melissa A. Reimers, Jacqueline T. Brown, Armelle Vinceneux, Daniel Castellano Gauna, Amita Patnaik, Nobuaki Matsubara, Loic Lebellec, Philippe Barthelemy, Kristen Renee Spencer, Nuria Kotecki, Alejandro Falcon Gonzalez, Craig Gedy, Kazuki Sudo, Hongmei Han, Kaity Aptaker, Traci Lynne Kelly, Jonathan E. Rosenberg; Massachusetts General Hospital, Harvard Medical School, Boston, MA; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, TX; Department of Internal Medicine, Washington University in St. Louis, St. Louis, MO; Winship Cancer Institute of Emory University and Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; Département de Cancérologie Médicale, Centre Léon-Bérard, Lyon, France; Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; The START Center for Cancer Research, San Antonio, TX; National Cancer Center Hospital East, Chiba, Japan; Medical Oncology Department, Centre Oscar Lambret, Lille, France; University Hospitals Strasbourg, Strasbourg, France; Laura & Isaac Perlmutter Cancer Center at NYU Langone Health, New York, NY; Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgium; Hospital Universitario Virgen del Rocío, Seville, Spain; ICON Cancer Center, Adelaide, SA, Australia; Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; Eli Lilly and Company, Indianapolis, IN; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Enfortumab vedotin plus pembrolizumab (EVP) is the current first-line standard of care for locally advanced / metastatic urothelial carcinoma (mUC). However, subsequent treatment options are limited, representing an urgent and growing unmet need. Preclinical data suggest that EV resistance may be payload mediated and consequently Nectin-4 remains a viable target for alternative therapies. LY4101174 is a next generation anti-Nectin-4 ADC comprising a humanized IgG1 antibody conjugated to the topoisomerase I inhibitor, exatecan, via a maleimide- β -glucuronide poly-sarcosine linker and a homogeneous drug antibody ratio of 8. Here, we report the initial clinical data from the phase 1 dose escalation cohort of EXCEED (NCT06238479). **Methods:** Adults with locally advanced / mUC or other selected solid tumors were eligible. Participants (pts) must have received or were ineligible for available standard therapies, and have ECOG PS 0-1. Dose escalation utilized a Bayesian optimal interval design. Key endpoints were safety, PK, and antitumor activity of LY4101174 per RECIST v1.1. **Results:** As of 3 Dec 2025, 143 pts (86 mUC, 57 non-UC tumors) were treated across 6 dose levels (DLs) of LY4101174 (0.8-3.2 mg/kg Q2W or 2.4-4.0 mg/kg Q3W IV). Median age was 68 (range, 30-85), 60% ECOG PS 1. Median prior lines of therapy was 4 (range, 1-10), 92% of mUC pts had received prior EV (19% [15/79] had discontinued EV due to treatment-related toxicity). LY4101174 and total antibody exhibited mostly linear, dose-proportional PK up to 4.0 mg/kg, and up to 3.2 mg for exatecan. At 3.2 mg/kg Q2W, 3 of 6 pts experienced DLTs (neutropenia [grades 3 and 4], febrile neutropenia, and thrombocytopenia [both grade 3]) prompting a schedule change to 3.2 mg/kg Q3W for continued escalation. The most common treatment-emergent AEs (TEAEs) across Q3W DLs were anemia (71%), fatigue (55%), nausea (49%), neutropenia (36%), thrombocytopenia (31%), diarrhea (26%), vomiting (25%), and decreased appetite (23%). The most common grade ≥ 3 TEAEs were anemia (47%), neutropenia (29%), thrombocytopenia (21%), febrile neutropenia and leukopenia (10% each); prophylactic granulocyte colony stimulating factor (G-CSF) was required at DL 4.0 mg/kg Q3W. TRAEs led to dose reduction in 24% and discontinuation in 2%. In the 66 efficacy evaluable mUC pts treated with 2.4-4.0 mg/kg Q3W (92% [61/66] EV-pretreated), ORR was 18% (12/66) and DCR was 70% (46/66) with 12 PR (8 confirmed, 4 ongoing and pending confirmation) and 34 SD. Median follow-up was 4.9 months (95% CI, 1.4-NE). **Conclusions:** LY4101174 has demonstrated clinical activity at Q3W dose levels, including in EV pre-treated mUC, suggesting Nectin-4 remains an important therapeutic target. Dose and duration on treatment were mainly limited by grade ≥ 3 hematologic toxicity requiring the use of prophylactic G-CSF. Clinical trial information: NCT06238479. Research Sponsor: Eli Lilly and Company.

Bulumtaturg fuvedotin (BFv; 9MW2821) plus toripalimab in patients with locally advanced or metastatic urothelial carcinoma (la/mUC): Follow-up results from a phase 1b/2 study.

Xinan Sheng, Shusuan Jiang, HongQian Guo, Bin Hu, Haiying Dong, Benkang Shi, Peng Zhang, Xin Yao, Tiejun Yang, Hang Huang, Manming Cao, Jingming Dong, Peipei Wang, Shuhai Wang, Jun Guo; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Hunan Cancer Hospital, Changsha, China; Department of Urology, Nanjing Drum Tower Hospital, Nanjing, China; Department of Urology, Liaoning Cancer Hospital & Institute, Shenyang, China; Department of Urology, Zhejiang Provincial People's Hospital, Hangzhou, China; Department of Urology, Qilu Hospital of Shandong University, Jinan, China; West China Hospital, Sichuan University, Chengdu, China; Tianjin Cancer Hospital, Tianjin, China; Department of Urology, The Affiliated Cancer Hospital of Zhengzhou University, 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; Mabwell (Shanghai) Bioscience Co., Ltd., Shanghai, China

Background: Nectin-4 is an adhesion molecule that is highly expressed in variety of solid tumors, especially in urothelial cancer, cervical cancer, esophageal cancer and breast cancer. BFv is a novel site-specific ADC targeting Nectin-4, and Toripalimab is a novel recombinant humanized anti-PD-1 monoclonal antibody. Previous results of BFv and Toripalimab in la/mUC patients have shown promising efficacy and well-tolerable toxicity. Here we report follow-up results of BFv and Toripalimab in la/mUC patients. **Methods:** This is an open-label, multicenter, phase 1b/2 study to evaluate the safety and efficacy of BFv combined with Toripalimab in la/mUC. Patients received BFv (1.0 or 1.25mg/kg) on D1/D8 and Toripalimab (240mg) on D1, 21 days per cycle. Primary objective was safety, and secondary objectives were efficacy, pharmacokinetics and immunogenicity. **Results:** As of 1 Dec 2025 (median follow-up time: 16.0 months), 47 assessable patients with la/mUC were enrolled and received the combination therapy of BFv and toripalimab. 7 of them (3 received BFv 1.0mg/kg; 4 received BFv 1.25mg/kg) have been previously treated for la/mUC and other 40 (all received BFv 1.25mg/kg) were treatment-naïve patients. In the overall population, ORR was 83.0% (95%CI 69.2–92.4), CR rate was 12.8%. All CR patients were still on treatment and the longest treatment duration has already exceeded two years. DCR was 89.4% (95%CI 76.9–96.5), median PFS was 12.9 months (95%CI 6.5–NA) and median DOR was not reach. Median OS also was not reach, OS rate at 18 months was 68.1% (95%CI 52.7–79.4). Subgroup analysis showed significant benefits to all patients, which might indicate that compared to traditional chemotherapy, BFv plus toripalimab could bring patients greater benefits and a longer survival time, especially in those elderly and patients with impaired kidney function. Safety profile was consistent with previous results, and there was no other new safety signals of BFv or toripalimab observed in this study. **Conclusions:** BFv plus toripalimab in patients with la/mUC demonstrated remarkable efficacy and well-tolerated safety profile. A pivotal phase 3 study is ongoing currently. Clinical trial identification: NCT06592326, NCT06079112. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

Microbial dysbiosis as predictor of benefit from CBM588 as an adjunct to immune checkpoint blockade (ICB)–based first line therapies in metastatic renal cell carcinoma (mRCC).

Rahul Winayak, Xinran Qi, Ali Moradi, Hedyeh Ebrahimi, Antonio Cruz Gomes, Miguel Zugman, Salvador Jaime-Casas, Xiaochen Li, Tanya B. Dorff, Joann Hsu, Alex Chehraz-Raffle, Motomichi Takahashi, Kentaro Oka, Seiya Higashi, Peter P. Lee, Thomas P. Parks, Jennifer Karmouch, Robert R. Jenq, Sumanta Kumar Pal, Nazli Dizman; City of Hope Comprehensive Cancer Center, Duarte, CA; Beth Israel Deaconess Medical Center, Boston, MA; Miyarisan Pharmaceutical Co., Ltd., Saitama, Japan; Osel Inc., Mountain View, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The *Clostridium butyricum*-based live biotherapeutic, CBM588, demonstrated signals for enhanced clinical activity with first-line ICB combinations in two randomized phase I trials for mRCC. However, impact of microbial dysbiosis on the benefit of CBM588 supplementation is unclear. Herein, we examined prognostic and predictive value of microbial dysbiosis with CBM588. **Methods:** We analyzed clinical outcomes and stool whole-genome sequencing data from a combined cohort from two randomized phase I clinical trials. Both enrolled treatment-naïve patients with mRCC and randomized them to receive nivolumab/ipilimumab (NCT03829111) or nivolumab/cabozantinib (NCT05122546) alone (standard of care [SOC]), or with CBM588 (SOC+CBM588). Baseline TOPOSCORE, a stool metagenomic dysbiosis index linked to ICB outcomes, was analyzed continuously (S score positively correlated with dysbiosis) and categorically (SIG1+ [dysbiosis phenotype] vs SIG2+ [non-dysbiosis]). Associations with progression free survival (PFS) and objective response rate (ORR, per RECIST 1.1) with SOC and SOC + CBM588 were assessed. **Results:** Fifty-nine patients were included: 39 in the SOC + CBM588 arm and 20 in the SOC arm. Median age was 65 (range 36–90), with the majority male (69.5%), clear-cell (88.1%) and intermediate/poor risk (67.8%) mRCC. Baseline clinical characteristics were comparable across arms. ORR was 66.7% in SOC+CBM588 arm versus 20.0% in the SOC arm ($p = 0.001$). Median PFS was 32.1 months (95% CI 16.6–NR) with SOC+CBM588 versus 3.7 months (95% CI 2.6–17.0) with SOC (HR 0.36 [95% CI 0.19, 0.67], $p = 0.001$). At baseline, S score was similar across arms ($p = 0.16$), and SIG1+ was seen in 55.6% of patients in the SOC+CBM588 arm versus 44.4% in the SOC arm ($p = 0.441$). While differences in PFS were not statistically significant in the SIG2+ cohort between SOC+CBM588 and SOC alone (32.0 vs 10.9 months, HR 0.49 [95% CI 0.19–1.3], $p = 0.149$), in the SIG1+ setting, a PFS improvement was seen for SOC+CBM588 versus SOC alone (24.9 vs 2.8 months, HR 0.19 [95% CI 0.07–0.53], $p < 0.001$). Notably, S score was associated with response to SOC+CBM588 among patients who received nivolumab/ipilimumab backbone (median S score 0.668 in response vs 0.540 in no response, $p = 0.046$), while no such association was observed in patients treated with nivolumab/cabozantinib backbone (median S score 0.681 vs 0.821, $p = 0.554$, respectively). **Conclusions:** Addition of CBM588 to ICB-based first-line combinations conferred a disproportionately greater benefit in patients with a dysbiotic stool phenotype, underscoring actionability of TOPOSCORE as a potential predictive biomarker in this setting. The upcoming phase III randomized placebo-controlled BIOFRONT trial will assess clinical activity of CBM588 and advance microbiome-based predictive biomarker development in mRCC. Research Sponsor: None.

Prospective clinical activity and preclinical basis of panitumumab-based EGFR blockade in SMARCB1-deficient renal medullary carcinoma (RMC): A collaborative multi-institutional study.

Pavlos Msaouel, Eric S. Rupe, Xinyue Chen, Ritesh R. Kotecha, Damian Tobias Rieke, Bradley Alexander McGregor, Najat C. Daw, Alice C. Fan, Eric Marshall Knoche, Christos Kyriakopoulos, Aly-Khan A. Lalani, Amartej Merla, Martin H. Voss, M. Neil Reaume, Alexander J. Lazar, Luisa Maren Solis, Bora Lim, Nizar M. Tannir, Menuka Karki, Niki Marie Zacharias; 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; Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Charité – Universitätsmedizin Berlin, Berlin, Germany; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, and Harvard Medical School, Boston, MA; Division of Oncology, Stanford University School of Medicine, Stanford, CA; Washington University School of Medicine, Division of Medical Oncology, St. Louis, MO; University of Wisconsin Carbone Cancer Center, Verona, WI; Department of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; City of Hope National Medical Center, Duarte, CA; Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; University of Ottawa, Ottawa, ON, Canada; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Breast Medical Oncology, Morgan Welch IBC Clinic and Research Program, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: RMC is a rare, exceptionally aggressive malignancy that predominantly affects young individuals of African descent with sickle cell trait. RMC is typically refractory to standard kidney cancer therapies, including anti-angiogenic agents and immune checkpoint inhibitors. While cytotoxic chemotherapy is the current standard, objective response rates (ORR) remain low (~29%), with a median progression-free survival (PFS) of ≤ 4 months in the first-line setting. This study explores wild-type EGFR as a therapeutic dependency in RMC. **Methods:** We characterized EGFR expression and mutation status in primary RMC tumors using whole exome sequencing (WES), CLIA-certified IHC and integrated bulk RNA and histone ChIP-sequencing. Preclinical efficacy was compared between the EGFR antibody panitumumab and the kinase inhibitor erlotinib across two RMC xenograft models. Subsequently, a prospective multi-national registry (N=26) evaluated panitumumab-based therapy (monotherapy or combined with nab-paclitaxel $\pm$ carboplatin) in heavily pretreated patients with RMC. **Results:** No EGFR mutations were detected on WES. RMC tumors demonstrated uniformly high wild-type EGFR protein expression and enhancer-associated activation. In vivo, panitumumab induced profound tumor regressions in both RMC xenograft models, significantly outperforming erlotinib ($p < 0.005$). Mechanistically, panitumumab triggered definitive lysosomal receptor degradation and suppressed AKT and ERK1/2 signaling. The prospective clinical registry (N=26) included 20 (76.9%) males and 6 (23.1%) females, with a median age of 33.5 years (range, 17–67). At treatment initiation, patients had a median of 4 metastatic disease sites (range, 2–6). The cohort was heavily pretreated with a median of 2 prior systemic therapies (range, 0–4); 96.2% had progressed on prior platinum-based chemotherapy. We observed an ORR of 53.9% (14/26 patients), including 4 (15.4%) complete responses. Median PFS was 5.8 months (95% CI: 4.0–8.2) and median OS was 9.5 months (95% CI: 7.6–NE). Treatment was well-tolerated, with manageable grade 1–2 acneiform rash (80.8%), no grade 3+ rash cases observed, and no treatment-related deaths. **Conclusions:** These data establish wild-type EGFR dependency as a foundational vulnerability in RMC. Panitumumab-based therapy yields unprecedented responses in heavily pretreated patients and represents a transformative new systemic standard of care for this lethal disease. Research Sponsor: National Cancer Institute; R37CA288448; National Cancer Institute; R01CA285454; National Cancer Institute; P30 CA016672.

Clinical outcomes.	
	Total (N=26)
Best overall response, n (%)	
Complete response	4 (15.4%)
Partial response	10 (38.5%)
Stable disease	7 (26.9%)
Progressive disease	5 (19.2%)
Depth of response %	
Median (IQR)	-30.9 (-58.9, +3.1)

Final results of a phase 2 trial of cabozantinib plus nivolumab (CaboNivo) in patients with non-clear cell renal cell carcinoma (nccRCC).

Darren R. Feldman, Martin H. Voss, Marie Carlo, Andrea Knezevic, Ying-Bei Chen, Robert A. Lefkowitz, Madison Perez, Kira vom Eigen, Nwamaka Okocha, Allura R. Wildman, Kelly N. Fitzgerald, Neil J. Shah, Emily Feld, Colette Ngozi Owens, Deaglan Joseph McHugh, David H. Aggen, Ritesh R. Kotecha, Andrew E. Cornish, Sahil D. Doshi, Robert J. Motzer; Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY; Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; University of California, San Francisco, San Francisco, CA; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: CaboNivo improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) over sunitinib in a phase 3 trial for metastatic clear cell RCC. (Choueiri NEJM 2021). We previously reported on 47 patients (pts) treated on a phase 2 trial of CaboNivo for nccRCC. We now present final results on all 60 pts accrued to the study. **Methods:** Pts had advanced nccRCC, 0 or 1 prior systemic therapies excluding prior immune checkpoint inhibitors and measurable disease by RECIST. Cabo 40 mg/day plus Nivo 240 mg every 2 weeks or 480 mg every 4 weeks was given across two cohorts. Cohort 1: papillary, unclassified, or translocation associated RCC (tRCC); Cohort 2: chromophobe RCC. The primary endpoint was ORR by RECIST; secondary endpoints included PFS, OS, and safety. Cohort 1 was a single stage design that met its primary endpoint and was expanded to produce more precise estimates of ORR. Cohort 2 was a Simon two-stage design that closed early for lack of efficacy and slow accrual. **Results:** Of 60 pts, 53 were included in Cohort 1, of whom 16 had papillary RCC, 16 unclassified RCC with papillary features (UCPF), 8 FH-deficient, 8 unclassified without papillary features (UC), and 5 tRCC. In Cohort 1, 39 (74%) pts were previously untreated, and 14 (26%) pts had 1 prior line: 10 (19%) received prior VEGF-targeted therapy and 8 (15%) received prior mTOR-targeted therapy. For Cohort 1 (Table), the ORR was 43% (95% CI 30–58), including 88% in pts with FH-deficient RCC. Median PFS (mPFS) in Cohort 1 was 11 months (95% CI 8–14), median OS was 28 months (95% CI 21–37), and there were 43 deaths after a median follow-up of 50 months for survivors. 7 pts with chromophobe RCC were enrolled in Cohort 2 with 5 achieving stable disease (SD) but no objective responses observed. Adverse events were similar to the previously reported cohort and cabozantinib and nivolumab were discontinued for toxicity in 22 (42%) and 20 (38%) pts, respectively. **Conclusions:** Final results from this phase 2 trial in nccRCC confirm efficacy and acceptable safety of CaboNivo in pts with metastatic papillary, unclassified, or tRCC histologies with a particularly high ORR in FH-deficient RCC. These results justify CaboNivo as a standard first-line treatment option for these pts. In contrast, objective responses were not observed in chromophobe RCC. Clinical trial information: NCT03635892. Research Sponsor: None.

Cohort 1 outcomes.

Outcome	All Pts (n=53)	1 st -line (n=39)	2 nd -line (n=14)	Papillary (n=16)	UCPF (n=16)	FH-def (n=8)	UC (n=8)	tRCC (n=5)
ORR, % (95% CI)	43 (30-58)	46 (30-63)	36 (13-65)	31 (11-59)	38 (15-65)	88 (47-100)	50 (16-84)	20 (1-72)
CR, n (%)	1 (2)	1 (3)	0	1 (6)	0	0	0	0
PR, n (%)	22 (42)	17 (44)	5 (36)	4 (25)	6 (38)	7 (88)	4 (50)	1 (20)
SD, n (%)	27 (51)	19 (49)	8 (57)	10 (63)	10 (62)	1 (12)	2 (25)	4 (80)
PD, n (%)	3 (6)	2 (5)	1 (7)	1 (6)	0	0	2 (25)	0
mPFS, mo. (95% CI)	11 (8-14)	11 (8-16)	14 (5-23)	11 (7-25)	10 (5-13)	16 (5-37)	8 (1-34)	14 (5-41)

Artificial intelligence (AI)–augmented analysis of quantitative circulating tumor DNA (ctDNA) burden and longitudinal kinetics to identify prognostic risk stratification in metastatic clear cell renal cell carcinoma (mccRCC).

Eric Martin, Eun-mi Yu, Laura Meili Linville, Annika Murthi, Hongkun Wang, Jeanny B. Aragon-Ching; Inova Schar Cancer Institute, Fairfax, VA; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

Background: The relevance of ctDNA burden and longitudinal kinetics in RCC remains poorly defined. We applied AI–based analysis of quantitative ctDNA trajectories to identify prognostically informative patterns beyond baseline detection. **Methods:** We analyzed patients with mcrRCC undergoing longitudinal tumor-informed ctDNA testing (Signatera) during first-line immune checkpoint inhibitor–based therapy. Quantitative ctDNA burden in mean tumor molecules per milliliter (MTM/mL) was measured serially and aligned to treatment initiation, with radiographic response classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). ctDNA trajectory similarity was independently assessed using dynamic time warping (DTW), trajectory-based K-means clustering, and a neural network sequence autoencoder (TensorFlow) with clustering to learn latent representations of ctDNA kinetics. Cross-method concordance was used to define robust ctDNA kinetic phenotypes. **Results:** Survival and response analyses included 93 patients with mcrRCC with longitudinal ctDNA profiling. Baseline ctDNA detectability was not significantly associated with OS. Conversion from ctDNA-positive to ctDNA-negative status during therapy was associated with improved OS ($p < 0.05$). Patients with radiographic disease control (CR/PR/SD) had significantly lower peak ctDNA levels than those with progressive disease (median 0.18 vs 8.86 MTM/mL; $p = 0.007$). Increasing peak ctDNA burden was strongly associated with inferior OS (HR 2.21, 95% CI 1.63–3.01; $p < 0.001$). A machine learning–based spline-regularized Cox survival model identified a high-risk ctDNA threshold > 20 MTM/mL associated with worse OS ($p = 0.034$). Trajectory-based K-means identified an optimal solution at $k = 4$ clusters, independently supported by DTW and autoencoder-based analyses. Four ctDNA kinetic phenotypes repeatedly emerged: early ctDNA clearance, early ctDNA rise, delayed ctDNA clearance, and persistently low-level ctDNA. Autoencoder-derived phenotypes demonstrated strong internal robustness (Adjusted Rand Index, ARI ≈ 0.80) and high concordance with DTW-based clustering. Phenotypes were associated with distinct radiographic response and survival patterns, with early ctDNA rise conferring the poorest OS ($p = 0.022$). **Conclusions:** AI-driven modeling of quantitative ctDNA burden and longitudinal kinetics identifies biologically interpretable and reproducible prognostic phenotypes in RCC, capturing higher-order temporal features of ctDNA dynamics and providing prognostic stratification beyond baseline detectability and burden alone, thereby informing clinical decision-making regarding earlier therapy switching. Research Sponsor: None.

Vessel branching patterns quantified by artificial intelligence as a novel prognostic biomarker in advanced renal cell carcinoma: A post-hoc analysis of the CM914 trial.

Hannah Timm, Marieta Toma, Julian Friedrich, Fabian Hörst, Niklas Klümper, Yangping Li, Alexander Effland, Michael Hölzel, Jens Kleesiek, Viktor Grünwald; Institute for AI in Medicine, University Hospital Essen, Essen, Germany; Institute of Pathology, University Hospital Bonn, Bonn, Germany; Institute for Artificial Intelligence in Medicine, University Hospital Essen, Essen, Germany; University Hospital Bonn, Bonn, Germany; Institute of Applied Mathematics, Bonn, Germany; Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany; Clinic for Medical Oncology and Clinic for Urology, University Hospital Essen, West German Cancer Centre, Essen, Germany

Background: Current adjuvant risk stratification in renal cell carcinoma (RCC) relies primarily on TNM-staging. However, disease progression and response to therapy are driven by biological subgroups reflected in tumor vessel architecture. We therefore analyzed vessel branching patterns in 1098 adjuvant RCC patients to evaluate whether an AI-derived biomarker quantifying vascular architecture improves prognostic discrimination beyond TNM. **Methods:** Digital images of representative tumor tissue and oncologic outcomes were obtained from the CM914 trial (NCT03138512). Tumor tissue was annotated by a pathologist to define vessel branching patterns as high-branching (HB) or low-branching (LB) patterns. HB and LB patterns were quantified using a deep learning model as the tumor-wide fraction of HB in digitized H&E whole-slide images from 1098 of 1641 evaluable patients (67%). Based on the tumor-wide HB fraction, patients were classified into risk groups using a data-driven cut-off optimized for Kaplan–Meier survival analysis, allowing comparison with TNM-based risk strata (PT2a, G3/G4, No, Mo / PT2b, G ANY, No, Mo / PT3, G ANY, No, Mo; intermediate-high risk, n=1016 vs PT4, G ANY, No, Mo / PT ANY, G ANY, N1, Mo; high risk, n=82). Risk stratification performance for overall survival (OS) and disease-free survival (DFS) was compared between branching pattern-based and TNM-based risk groups using Cox regression, Kaplan–Meier analysis, and concordance indices. **Results:** Higher tumor-wide HB fractions were associated with improved DFS and OS, showing a continuous effect on prognosis. Each 10% increase in HB fraction reduced risk of recurrence and death (DFS HR 0.92, 95% CI 0.89–0.95; OS HR 0.89, 95% CI 0.83–0.95; both $p<0.005$). Kaplan–Meier analyses showed longest survival in the 4th quartile (OS HR 0.39, 95% CI 0.21–0.71, $p=0.002$; DFS HR 0.47, 95% CI 0.35–0.64, $p<0.0001$). This threshold defined the 75th percentile cutoff for risk stratification, separating patients into intermediate risk ($\geq 74\%$ HB; n=275) vs high risk ($<74\%$ HB; n=823) groups. High risk patients had an increased risk of recurrence and death (DFS HR 2.11, 95% CI 1.57–2.84, C-Index 0.57; OS HR 2.57, 95% CI 1.28–4.32, C-Index 0.56, both $p<0.005$). TNM-based risk showed lower prognostic discrimination (DFS: HR 1.95, 95% CI 1.39–2.74, C-Index 0.53; OS: HR 2.55, 95% CI 1.52–4.30, C-Index 0.55, both $p<0.005$). Combining branching-based risk with TNM improved DFS and OS discrimination compared with TNM alone (C-Index 0.59). **Conclusions:** Higher fractions of high-branching vessels are associated with improved DFS and OS, potentially enabling risk stratification beyond conventional TNM criteria in RCC. While prospective validation is required to confirm clinical applicability, these results suggest high-branching vessel architecture represents a promising prognostic feature. Research Sponsor: None.

Deciphering the genomic landscape of renal cell carcinoma brain metastases.

Betul Gok Yavuz, Peng Li, Jose A. Ovando-Ricardez, Alessandro La Ferlita, Jonathan W. T. Tse, Sahin Hanalioglu, Berrin Babaoglu, Baylar Baylarov, Lisa M. Norberg, Haidee Chancoco, Erika Thompson, Melike Mut, Figen Soylemezoglu, Jason T. Huse, Adeboye O. Osunkoya, Mehmet Asim Bilen, Merve Hasanov, Eric Jonasch, David J. H. Shih, Elshad Hasanov; The University of Chicago, Chicago, IL; Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; The Ohio State University, Columbus, OH; The University of Hong Kong, Hong Kong, China; Hacettepe University Faculty of Medicine, Ankara, Turkey; Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Virginia Health System, Charlottesville, VA; Departments of Pathology and Urology, Emory University School of Medicine, Atlanta, GA; Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; School of Biomedical Science, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

Background: Brain metastases from renal cell carcinoma (RCC) remain a major cause of morbidity and mortality, yet the drivers of metastatic dissemination remain poorly understood.

Methods: Whole-exome sequencing was performed on 72 RCC brain metastasis samples with matched normal. To identify candidate metastatic drivers, the genetic alterations detected in the brain metastases were compared against alterations in extracranial metastases from the MSK-ECM cohort (n=137) and primary RCC tumors from TCGA (n=432) by case-control analyses. Candidate drivers were also identified by matched-pair analyses on the brain metastases vs. matched primary tumors or extracranial metastases from the same patient (n=25). A random survival forest model incorporating the candidate CNA events was developed to predict overall survival. The candidate metastatic drivers were further evaluated using functional experimental data from MetMap and DepMap. Survival analyses were conducted to assess the prognostic significance of the candidate drivers. **Results:** We identified metastatic drivers that were significantly enriched in RCC brain metastases, including 4q loss, 7p gain, 7q gain, 8p loss, 8q gain, 9p21.3 deletion, 12q15 amplification, and 14q loss. These driver events were associated with significantly poorer patient survival among RCC patients. A random survival forest model based on these CNA events stratified TCGA-KIRC patients into prognostically distinct risk groups (C-index = 0.64). Among the drivers, 8p loss, 8q gain, 9p21.3 deletion were associated with increased incidence of brain metastases across multiple primary cancer types in xenograft mouse models. These drivers were also strongly associated with metastatic progression and poor prognosis across RCC, lung adenocarcinoma, breast cancer, and melanoma.

Conclusions: Somatic copy-number alterations represent key drivers of brain metastasis in RCC and other tumors that frequently metastasize to the brain. These findings indicate a shared genomic basis for brain tropism across cancers and highlight the potential utility of copy-number biomarkers for risk stratification and clinical decision-making. Research Sponsor: Pelotonia Institute for Immuno-Oncology Recruitment Startup Fund; Society for Immunotherapy of Cancer-NanoString Technologies Single Cell Biology Award; International Kidney Cancer Coalition Cecile and Ken Youner Scholarship; Kidney Cancer Association Young Investigator Award; Gateway Cancer Research Foundation; American Society of Clinical Oncology Conquer Cancer Foundation Young Investigator Award.

CheckMate-901: Association of tumor and peripheral biomarker profiles with durable disease control in metastatic urothelial carcinoma treated with nivolumab plus ipilimumab.

Matthew D. Galsky, Guru P. Sonpavde, Michiel S. Van Der Heijden, Thomas Powles, Akshay Yadav, Diego G. Chowell, Jeiry Filian, Lily Wang, Saurabh Gupta; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Netherlands Cancer Institute, Amsterdam, Netherlands; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Bristol Myers Squibb, Hyderabad, India; Icahn School of Medicine at Mount Sinai, New York, NY; Bristol Myers Squibb, Princeton, NJ

Background: Patients (pts) with untreated, unresectable, or metastatic urothelial carcinoma (mUC) have limited therapeutic options and poor prognosis. The phase 3, global, open-label, randomized CheckMate 901 trial compared nivolumab plus ipilimumab (NIVO+IPI) vs gemcitabine–carboplatin/gemcitabine–cisplatin (gem–carbo/gem–cis) with previously untreated unresectable or mUC. A subset of pts treated with NIVO+IPI experienced durable disease control. This exploratory analysis seeks to identify biomarkers that might characterize pts deriving particular benefit from NIVO+IPI. **Methods:** Serum samples from CheckMate 901 (NIVO+IPI, n = 288–300; gem–carbo/gem–cis, n = 222–236) underwent multiplex analysis at Myriad RBM using Luminex and Simoa technology. Pts were stratified by progression-free survival (<8 months [early progressor; EP] vs ≥8 months [durable benefit; DB]), and clinical laboratory variables (granulocyte count [GRANC], hemoglobin [HB], thyroid-stimulating hormone [TSH], neutrophil-lymphocyte ratio [NLR]) and cytokine/protein biomarkers (alpha-1 antitrypsin [AAT], beta2-microglobulin [B2M], C-reactive protein [CRP], ferritin [FRTN], interleukin [IL]-2 receptor alpha [IL-2ra], IL-8, vascular cell adhesion molecule-1 [VCAM-1], and von Willebrand factor [vWF]) were compared in EP vs DB pts. In addition, tumor RNA-seq was used for gene signature analysis (NIVO+IPI, n = 134; gem–carbo/gem–cis, n = 117), including 8-gene epithelial–mesenchymal transition (EMT)/stroma core, 9-gene transforming growth factor beta (TGFβ) activation, 13-gene high-risk TGFβ, and cluster of differentiation 4 (CD4). **Results:** Distinct biomarker patterns emerged between EP and DB pts. Pts achieving DB vs EP with NIVO+IPI exhibited significantly lower levels of GRANC, TSH, and NLR, and higher HB (all $P < 0.05$). Similarly, levels of proteins AAT, B2M, CRP, FRTN, IL-2ra, IL-8, VCAM-1, and vWF were significantly lower in NIVO+IPI-treated pts achieving DB vs EP (all $P < 0.05$). RNA-seq analysis showed significant differences between NIVO+IPI-treated pts achieving DB vs EP for 8 EMT/stroma core and 9 TGFβ activation ($P < 0.05$). **Conclusions:** In untreated, unresectable, or mUC, distinct clinical and cytokine/protein biomarker profiles were associated with DB vs EP with NIVO+IPI therapy. Pts with EP exhibit features in the tumor microenvironment and circulation suggestive of tumor-promoting inflammation, several of which have been linked to resistance to immune checkpoint blockade in prior analyses. These findings underscore the heterogeneity of mUC and the potential of routinely measured circulating analytes for risk stratification and treatment decisions. Prospective studies should confirm their clinical applicability. Clinical trial information: NCT03036098. Research Sponsor: Bristol Myers Squibb.

Machine learning–based transcriptomic signatures to predict treatment outcomes across targeted and immunotherapy regimens in renal cell carcinoma.

Peng Li, Zuhair Majeed, Semiha Ozgul, Mostafa I.H. Ali, Nancy Single, Daniel G. Stover, Mina S. Makary, Fuat Bicer, Amir Mortazavi, W. Kimryn Rathmell, Eric A. Singer, Khalid Niazi, Richard Cheng Han Wu, Merve Hasanov, Elshad Hasanov; Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Ohio State University, Columbus, OH; Comprehensive Cancer Center & James Solove Research Inst., The Ohio State University Medical Center, Columbus, OH; The Ohio State University Comprehensive Cancer Center, Columbus, OH; The Ohio State University, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, OH; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Department of Urology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Department of Pathology, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Despite available tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), reliable biomarkers guiding frontline advanced RCC treatment remain limited. Existing signatures lack generalizability across therapeutic regimens. We developed a data-driven machine learning (ML) framework to predict survival outcomes and therapeutic response. **Methods:** Transcriptomic and clinical data were analyzed from 733 patients across two frontline treatment cohorts, sunitinib ($n = 376$) and avelumab plus axitinib ($n = 357$), derived from JAVELIN Renal 101. A multi-algorithm feature selection framework was applied to identify transcriptomic signatures associated with progression-free survival (PFS) and overall survival (OS). Prognostic performance was evaluated using the concordance index (C-index). Predictive models for therapeutic response, including disease control, were developed using PFS-derived gene signatures and assessed by area under the curve (AUC). External validation was performed in an independent cohort from The Ohio State University Total Cancer Care (OSU TCC) ($n = 114$). **Results:** ML-derived transcriptomic models consistently stratified patients into distinct risk groups with improved prognostic discrimination compared with standard clinical classifiers. In the sunitinib cohort, the best-performing models achieved C-indices of 0.72 for PFS and 0.81 for OS, outperforming IMDC (0.59 and 0.66). In the validation set of the sunitinib cohort, high-risk patients exhibited worse outcomes, with hazard ratios of 3.00 for PFS ($P < 0.001$, 95% CI, 2.06–4.39) and 13.42 for OS ($P < 0.001$, 95% CI, 7.78–23.13). In the avelumab plus axitinib cohort, C-indices reached 0.70 for PFS and 0.79 for OS. Consistent risk stratification was observed in the validation set, with hazard ratios of 3.16 for PFS ($P < 0.001$, 95% CI, 2.07–4.83) and 4.69 for OS ($P < 0.001$, 95% CI, 2.65–8.30). For response prediction, the models demonstrated predictive performance, with the Naive Bayes model achieving a validation AUC of 0.83 for disease control in both sunitinib and avelumab plus axitinib cohorts. The model showed significant risk stratification in an external validation cohort (OSU TCC). **Conclusions:** This study presents a multi-cohort transcriptomic framework with prognostic and predictive utility in advanced RCC. By outperforming established clinical risk classifiers and enabling prediction of regimen-specific therapeutic responses, this ML-based approach supports biomarker-informed frontline treatment selection. Research Sponsor: The Ohio State University Comprehensive Cancer Center (OSUCCC); Pelotonia Institute for Immuno-Oncology (PIIO).

Efficacy outcomes by patterns of progression in patients with advanced renal cell carcinoma from the phase 3 CLEAR trial.

Viktor Grünwald, Daniel Keizman, Jens Bedke, Manuela Schmidinger, Michael D. Staehler, Saby George, Thomas E. Hutson, Ulka N. Vaishampayan, Jaime R. Merchan, Masatoshi Eto, Tom Samuel Waddell, Philippe Barthelemy, John Haanen, Joseph E. Burgents, Min Ren, Ian Brown, Chinyere E. Okpara, Bradley Alexander McGregor, Camillo Porta, Robert J. Motzer; University Hospital Essen, Essen, Germany; Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; Department of Urology and Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; Medical University of Vienna, Vienna, Austria; Hospital of Munich, Munich, Germany; Roswell Park Cancer Institute, Buffalo, NY; Texas Tech University Health Science Center School of Medicine, Lubbock, TX; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; University of Miami/ Sylvester Comprehensive Cancer Center, Miami, FL; Kyushu University, Fukuoka, Japan; The Christie NHS Foundation Trust, Manchester, United Kingdom; University Hospital Strasbourg, Strasbourg, France; Netherlands Cancer Institute, Amsterdam, Netherlands; Merck & Co., Inc., Rahway, NJ; Eisai Inc., Nutley, NJ; Eisai Ltd., Hatfield, United Kingdom; Dana-Farber Cancer Institute, Boston, MA; University of Bari "A. Moro" and Policlinico Consorziale di Bari, Bari, Italy; Memorial Sloan Kettering Cancer Center, New York, NY

Background: In CLEAR, lenvatinib + pembrolizumab (L+P) significantly improved efficacy vs sunitinib (S) in treatment-naïve patients with advanced renal cell carcinoma (Motzer 2021, Motzer 2024). We summarize efficacy by patterns of progressive disease (PD) for the L+P arm and report survival per a modified PD classification system (based on patients receiving immunotherapy; data cutoff 31 July 2022). **Methods:** Treatment-naïve patients (n=1069) who had clear-cell advanced renal cell carcinoma were randomized (1:1:1) to receive: L 20 mg PO daily + P 200 mg IV Q3W; or L + everolimus; or S 50 mg PO daily (4 wks on/2 wks off). Methods for post-progression survival/OS analyses were previously reported (Grünwald 2025). A modified system of classifying PD (Saal 2025) is used in new analyses of the L+P arm reported here: low risk (progression of existing lesions); intermediate risk (new lesions without progression of existing lesions); high risk (progression of existing lesions + new lesions). The number of patients with PD was determined by independent imaging review at the data cutoff date. **Results:** At the time of PD, the median tumor burden of target lesions was lower with L+P (−48.1%) vs S (−17.4%). Patients in the L+P arm with larger % decreases in sums of target lesion diameters at PD had longer median post-progression survival (≤−61% [n=59], 35.6 mos [95% CI 28.4–39.2]; >−61%–≤−34% [n=58], 24.4 mos [95% CI 15.5–34.5]; >−34% [n=59], 20.2 mos [95% CI 16.4–26.9]) and OS (Grünwald 2024, 2025). In the L+P arm, most patients had low/intermediate risk PD (Table). Patients with low (HR 0.39; 95% CI 0.22–0.70) or intermediate risk (HR 0.47; 95% CI 0.27–0.81) PD had improved OS vs patients with high risk PD. Patients with low/intermediate risk PD stayed on 1st subsequent anticancer medication longer than patients with high risk PD (Table). **Conclusions:** In the L+P arm, PD was mainly characterized by progression of existing lesions or formation of new lesions without progression of existing lesions (low/intermediate risk PD); these patients had improved OS (vs high risk PD) suggesting prognostic/predictive value of patterns of PD. Patients with low/intermediate risk PD stayed on 1st subsequent anticancer medication longer than patients with high risk PD, implying that 2L therapy can be used effectively upon progression with L+P. These results, together with lower tumor burden seen at PD in the L+P arm (Grünwald 2024), indicate that L+P has robust tumor control, supporting its use as a standard 1L therapy in advanced renal cell carcinoma. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Low risk PD (n=69)	Intermediate risk PD (n=91)	High risk PD (n=30)
Patients with any subsequent systemic anticancer medication during survival follow-up, n (%)	49 (71.0)	58 (63.7)	15 (50.0)
Time to discontinuation of 1 st anticancer medication during survival follow-up, median (Q1, Q3) (months)	14.4 (5.6, not estimable)	7.3 (3.1, 20.3)	4.3 (1.5, 13.7)

Included data is from the L+P arm.

Cabozantinib plus nivolumab (C+N) versus sunitinib (S) in patients with advanced renal cell carcinoma (aRCC) and bone metastasis: Updated subgroup analysis of the phase 3 CheckMate-9ER trial.

Andrea B. Apolo, Bernard Escudier, Thomas Powles, Maria T. Bournon, Cristina Suárez, Camillo Porta, Saby George, Toni K. Choueiri, Robert J. Motzer, Joshua Zhang, Denise Svendsgaard Williamson, Lana Andrianova, Jose Ricardo Perez, Tasha D. Hall, Amishi Yogesh Shah; National Cancer Institute, National Institutes of Health, Bethesda, MD; Gustave Roussy, Villejuif, France; Barts Cancer Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, United Kingdom; Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; A. Moro University of Bari and Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Bristol Myers Squibb, Princeton, NJ; Exelixis, Inc., Alameda, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In first-line aRCC, C+N significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in the phase 3 CheckMate 9ER trial (NCT03141177; Motzer et al. *Ann Oncol* 2026). In an exploratory analysis with median 18.1-mo f-u, C+N improved PFS, OS, and ORR vs S in patients with or without bone metastasis at baseline. We performed an updated exploratory analysis of outcomes by baseline bone metastasis status based on the 5-year update and analyzed subgroups with additional metastatic sites. **Methods:** 651 patients with clear-cell aRCC were randomized 1:1 to C (40 mg QD) + N (240 mg Q2W) or S (50 mg QD for 4 weeks of 6-week cycles). Median f-u was 67.6 mo. PFS (primary endpoint) and ORR were per RECIST v1.1 by blinded independent central review. Patient subgroups analyzed here include those with or without bone metastasis at baseline and those with liver, lung, lymph node (LN), or adrenal gland metastasis in addition to bone metastasis. **Results:** 154 patients had bone metastasis at baseline. Baseline characteristics were generally consistent between treatment arms for subgroups with and without bone metastasis. PFS and OS were prolonged with C+N vs S in patients with or without bone metastasis (Table). The ORR was higher and duration of response (DOR) was longer with C+N vs S in both groups. Although outcomes were less favorable in those with vs without bone metastasis, the relative benefit with C+N vs S was consistent across metastatic site subgroups. The safety profile among patients with bone metastasis was generally consistent with the overall population. **Conclusions:** With additional follow-up, a consistent benefit was maintained for C+N vs S in patients with or without bone metastasis. Among patients with bone metastasis, a consistent benefit was observed regardless of concomitant metastasis in liver, lung, LN, or adrenal gland. Clinical trial information: NCT03141177. Research Sponsor: Exelixis, Inc.

Efficacy by metastatic sites.

Subgroup (C+N v S)	Bone + Any Site(s) ^a (n=79 v n=75)	No Bone (n=244 v n=253)	Bone + Liver (n=15 v n=17)	Bone + Lung (n=57 v n=58)	Bone + LN (n=33 v n=38)	Bone + Adrenal Gland (n=10 v n=8)
mPFS, mo	13.8 v 5.3 ^b	16.6 v 9.5	6.9 v 3.8	10.0 v 4.4	9.0 v 4.1	15.2 v 5.7
PFS HR (95% CI)	0.43 (0.30, 0.64) ^b	0.60 (0.49, 0.74)	0.77 (0.33, 1.76)	0.45 (0.29, 0.70)	0.50 (0.29, 0.87)	0.62 (0.19, 2.07)
mOS, mo	34.8 v 20.7 ^b	49.5 v 41.0	20.9 v 12.7	31.6 v 22.1	21.3 v 17.5	54.4 v 31.0
OS HR (95% CI)	0.66 (0.45, 0.95) ^b	0.85 (0.68, 1.06)	0.57 (0.26, 1.24)	0.72 (0.47, 1.10)	0.72 (0.43, 1.20)	0.72 (0.21, 2.50)
ORR, %	49 v 9 ^b	58 v 33	40 v 18	51 v 10	42 v 5	70 v 13
mTTR, mo	2.9 v 7.3	2.8 v 4.3	2.9 v 3.0	2.8 v 5.7	2.9 v 3.4	4.0 v 11.0
mDOR, mo	18.0 v 6.9	22.9 v 15.4	12.6 v 6.4	18.0 v 6.7	16.7 v NC	14.4 v 19.3

^aOnly 9 patients had bone-only disease (n=7, C+N; n=2, S), precluding meaningful analysis of this subgroup.

^bMotzer et al. *Ann Oncol* 2026. m, median; NC, not calculable; TTR, time to response.

An external validation of the IMmotion151 molecular subtypes in patients with advanced renal cell carcinoma using the ORIEN database.

Gautham Prakash, Nandan Srinivasa, Joslyn Jung, Anwaruddin Mohammad, Pankaj Kumar, Stefan Bekiranov, William Paul Skelton IV; University of Virginia, Division of Hematology/Oncology, Charlottesville, VA; Department of Medicine, University of Virginia, Charlottesville, VA; University of Virginia School of Medicine, Charlottesville, VA; Bioinformatics Core, University of Virginia, Charlottesville, VA; Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA

Background: There is a major unmet need for novel biomarkers in advanced renal cell carcinoma (RCC). A promising candidate biomarker is the classification of advanced RCC into 7 distinct molecular subtypes identified in an exploratory analysis of the IMmotion151 trial (Motzer et al., Cancer Cell 2020). These transcriptomic clusters were predictive of treatment outcomes with atezolizumab + bevacizumab vs sunitinib. However, a recent validation study reported that while these clusters were able to be replicated in an external cohort, they failed to stratify survival between avelumab + axitinib vs sunitinib (Saliby et al., Cancer Cell 2024). Given these mixed results, there is a need for further validation of the IMmotion151 molecular clusters. We used a multi-institutional cohort from the Oncology Research Information Exchange Network (ORIEN), an alliance of cancer centers, to replicate these clusters and assess if they were prognostic for 5-year overall survival (OS) in patients with advanced RCC. **Methods:** Patients with RCC metastatic to lymph nodes or a distant site were identified in the ORIEN database. Included patients had mRNA sequencing data available from a metastatic tumor sample. We used methods similar to those used in the IMmotion151 exploratory analysis to attempt to replicate the molecular clusters. Using an unsupervised clustering algorithm called non-negative matrix factorization (NMF) on the top 10% most variable genes in each sample, we derived 7 distinct molecular clusters. To compare our clusters with those identified in IMmotion151, we constructed a heatmap of expression (using z-scores) for pre-specified gene sets across each cluster. We then conducted Kaplan-Meier analysis to assess if our clusters were able to stratify 5-year OS in our patient cohort for a significance level of $p \leq 0.05$. OS was measured from the time of diagnosis with metastatic RCC. **Results:** 155 eligible patients were included in our analysis. We successfully replicated clusters 2 (angiogenic), 3 (complement/ Ω -oxidation), 4 (T-effector/proliferative), and 6 (stromal/proliferative). Cluster 7 (snoRNA) was not possible to replicate as our transcriptomic data only included mRNA. Kaplan-Meier analysis did not show any statistically significant difference ($p = 0.85$) in 5-year OS between our 7 clusters. Cluster 2 had a median OS of 47.5 months, cluster 3 had a median OS of 43.6 months, median OS was not reached for cluster 6, and there were insufficient patients in cluster 4 to be included in the survival analysis. **Conclusions:** While our results show that the IMmotion151 molecular subtypes are robust and replicable even in smaller datasets, the lack of any association between subtypes and survival outcomes casts further doubt on the clinical utility of these biomarkers. Our results may also be influenced by our smaller sample size compared to the IMmotion151 analysis ($n = 823$). Research Sponsor: Division of Hematology/Oncology, University of Virginia.

Cabozantinib plus nivolumab (C+N) versus sunitinib (S) in patients with advanced renal cell carcinoma (aRCC) and liver metastasis: Subgroup analysis of the phase 3 CheckMate-9ER trial.

Amishi Yogesh Shah, Bernard Escudier, Thomas Powles, Maria T. Bourlon, Cristina Suárez, Camillo Porta, Saby George, Toni K. Choueiri, Robert J. Motzer, Joshua Zhang, Denise Svendsgaard Williamson, Lana Andrianova, Jose Ricardo Perez, Tasha D. Hall, Andrea B. Apolo; The University of Texas MD Anderson Cancer Center, Houston, TX; Gustave Roussy, Villejuif, France; Barts Cancer Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, United Kingdom; Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; A. Moro University of Bari and Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Bristol Myers Squibb, Princeton, NJ; Exelixis, Inc., Alameda, CA; National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: In the phase 3 CheckMate 9ER trial (NCT03141177), C+N treatment significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in patients with first-line aRCC, including those with baseline LM (Motzer et al. *Ann Oncol* 2026). We performed exploratory analyses of outcomes in additional subgroups including patients with no LM (NLM) and those with LM plus other metastatic sites. **Methods:** 651 patients with clear-cell aRCC were randomized 1:1 to C (40 mg QD) + N (240 mg Q2W) or S (50 mg QD for 4 weeks of 6-week cycles). PFS (primary endpoint) and ORR were per RECIST v1.1 by blinded independent central review. Median f-u was 67.6 mo. Patient subgroups analyzed included those with LM or NLM at baseline and those with bone, lung, lymph node (LN), or adrenal gland metastasis in addition to LM. **Results:** 129 patients had LM at baseline. Baseline characteristics were generally consistent between treatment arms among patients with LM and NLM. A PFS and OS benefit with C+N vs S was observed in patients with LM and NLM (Table). Both subgroups experienced greater ORR and longer duration of response (DOR) with C+N vs S. Although outcomes were less favorable in those with vs without LM, and least favorable in those with both LM and bone metastasis, the relative benefit with C+N vs S was consistent across metastatic site subgroups. The safety profile among patients with LM was generally consistent with the overall population. Presence of LM did not negatively impact C dose exposure (median daily dose 31.8 mg in LM; 26.3 mg in NLM). **Conclusions:** Treatment with C+N vs S improved efficacy outcomes in patients with first-line aRCC irrespective of LM at baseline. Among patients with LM, a consistent benefit was observed regardless of concomitant metastasis in bone, lung, LN, or adrenal gland. Clinical trial information: NCT03141177. Research Sponsor: Exelixis, Inc.

Efficacy by metastatic sites.

Subgroup (C+N v S)	LM + Any Site(s) ^a (n=73 v n=56)	NLM (n=250 v n=272)	LM + Bone (n=15 v n=17)	LM + Lung (n=46 v n=43)	LM + LN (n=31 v n=27)	LM + Adrenal Gland (n=8 v n=6)
mPFS, mo	10.9 v 6.2 ^b	18.4 v 9.2	6.9 v 3.8	9.1 v 4.1	9.7 v 6.2	32.0 v 2.0
PFS HR (95% CI)	0.55 (0.37, 0.82) ^b	0.59 (0.48, 0.71)	0.77 (0.33, 1.76)	0.50 (0.32, 0.80)	0.65 (0.36, 1.17)	0.18 (0.04, 0.78)
mOS, mo	37.6 v 22.1 ^b	49.5 v 39.7	20.9 v 12.7	40.1 v 13.4	34.8 v 13.4	46.3 v 2.0
OS HR (95% CI)	0.65 (0.43, 0.97) ^b	0.83 (0.66, 1.03)	0.57 (0.26, 1.24)	0.49 (0.30, 0.79)	0.59 (0.33, 1.05)	0.10 (0.02, 0.53)
ORR, %	52 v 21 ^b	57 v 29	40 v 18	52 v 23	48 v 19	88 v 17
mTTR, mo	2.8 v 4.0	2.8 v 5.4	2.9 v 3.0	2.8 v 3.5	2.8 v 4.1	2.8 v 11.1
mDOR, mo	20.7 v 17.8	22.1 v 15.2	12.6 v 6.4	23.1 v 15.8	33.0 v 17.9	41.5 v NR

^aOnly 7 patients had liver-only disease (n=2, C+N; n=5, S), precluding meaningful analysis of this subgroup.

^bMotzer et al. *Ann Oncol* 2026. m, median; NR, not reached; TTR, time to response.

Efficacy of fruquintinib (F) plus sintilimab (S) versus axitinib (A) or everolimus (E) by scores of IMDC risk factors and PD-L1 expression at baseline in previously treated advanced renal cell carcinoma (RCC): A subgroup analysis of the FRUSICA-2 study.

Kaiwei Yang, Dingwei Ye, Xiaodong Zhang, Xin Yao, Yu Xie, Jianming Guo, Jing Li, Bin Hu, Jiasheng Bian, Chaochao Liang, Jun Xiao, Nian-Zeng Xing, Lulin Ma, Xiaoping Zhang, Zhenhua Liu, Hui Chen, Qing Zou, Chuize Kong, Panfeng Tan, Zhisong He; Department of Urology, Peking University First Hospital, Beijing, China; Fudan University Shanghai Cancer Center, Shanghai, China; Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Hunan Cancer Hospital, Changsha, China; Zhongshan Hospital, Fudan University, Shanghai, China; Henan Cancer Hospital, Zhengzhou, China; Department of Urology, Liaoning Cancer Hospital & Institute, Shenyang, China; Department of Urology, Cancer Hospital of Shandong First Medical University, Jinan, China; The First Affiliated Hospital of Anhui Medical University, Hefei, China; The First Affiliated Hospital of USTC Anhui Provincial Hospital, Hefei, China; Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union, Beijing, China; Peking University Third Hospital, Beijing, China; Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China; West China Hospital of Sichuan University, Chengdu, China; Harbin Medical University Cancer Hospital, Harbin, China; Jiangsu Cancer Hospital, Nanjing, China; The First Hospital of China Medical University, Shenyang, China; HUTCHMED Limited, Shanghai, China; The First Hospital of Peking University, Beijing, China

Background: FRUSICA-2 (NCT05522231), a randomized, open-label, controlled phase 2/3 study, demonstrated a significant efficacy of F plus S vs A or E in previously treated advanced RCC (BIRC-assessed mPFS 22.21 vs 6.90 mo; HR 0.373, $p < 0.0001$; ORR 60.5% vs 24.3%, OR 4.622, $p < 0.0001$; D Ye, et al; 2025 ESMO). Given the IMDC classification as the most common prognostic model and PD-L1 expression has demonstrated prognostic value across various cancer types, we conducted this exploratory subgroup analysis to evaluate clinical outcomes by baseline scores of IMDC risk factors and PD-L1 expression. **Methods:** Patients (pts) with histologically confirmed advanced RCC previously treated with VEGFR-TKI were randomized 1:1 to receive either F (5 mg QD, 2 weeks on/1 week off) plus S (200 mg iv, every 3 weeks), or investigator's choice of A (5 mg twice daily) or E (10 mg once daily). Efficacy was analyzed by IMDC risk factor scores (0, 1, 2, and ≥ 3) and PD-L1 combined positive score (CPS ≥ 1 , < 1 , or unknown). Data cutoff was February 17, 2025. **Results:** Among 234 patients in the phase 3 part, IMDC risk scores and PD-L1 CPS distributions are detailed in table. With a median follow-up of 16.56 mo, BIRC-assessed mPFS for F+S vs A/E across IMDC subgroups were: score 0, not estimable(NE) vs 8.31 mo (stratified HR 0.270, $p = 0.0009$); score 1, 24.87 vs 8.25 mo (HR 0.289, $p < 0.0001$); score 2, 13.8 vs 6.9 mo (HR 0.436, $p = 0.0164$); and score ≥ 3 , 9.69 vs 4.21 mo (HR 0.591, $p = 0.3267$). Across PD-L1 expression subgroups, BIRC-assessed mPFS for F+S vs A/E were: CPS ≥ 1 , 22.21 vs 3.22 mo (stratified HR 0.232, $p = 0.0004$); CPS < 1 , NE vs 8.28 mo (HR 0.350, $p < 0.0001$). An additional 82 patients had unknown PD-L1 CPS status (F+S: $n = 40$; A/E: $n = 42$) and were not included in PD-L1 subgroup analysis. ORR analyses consistently favored F+S over A/E across all subgroups defined by IMDC risk factors and PD-L1 expression, with detailed results presented in table. **Conclusions:** In the exploratory analyses, these findings suggest that the efficacy benefit of F+S vs A/E is maintained across different IMDC risk scores and PD-L1 CPS in previously treated advanced RCC patients, supporting its broad application. Clinical trial information: NCT05522231. Research Sponsor: HUTCHMED Limited.

Efficacy results by IMDC risk scores and PD-L1 expression.

	IMDC score 0 (33 v 32)	IMDC score 1 (43 v 41)	IMDC score 2 (30 v 31)	IMDC score ≥ 3 (13 v 11)	PD-L1 CPS ≥ 1 (23 v 20)	PD-L1 CPS < 1 (56 v 53)
F+S v A/E						
mPFS mo	NE v 8.31	24.87 v 8.25	13.80 v 6.90	9.69 v 4.21	22.21 v 3.22	NE v 8.28
HR (95%CI)	0.27 (0.12, 0.62)	0.29 (0.15, 0.55)	0.44 (0.22, 0.88)	0.59 (0.20, 1.72)	0.23 (0.10, 0.56)	0.35 (0.20, 0.61)
Unstratified Log-rank p	0.0009	< 0.0001	0.0164	0.3267	0.0004	< 0.0001
ORR, %	63.6 v 25.0	62.8 v 26.8	60.0 v 19.4	46.2 v 27.3	78.3 v 10.0	64.3 v 35.8
Odds Ratio (95%CI)	5.25(1.61, 17.71)	4.60(1.66, 12.98)	6.25(1.75, 23.80)	2.29(0.32, 19.10)	32.40(4.67, 338.60)	3.22(1.37, 7.61)

Emotional health concerns due to kidney cancer (KC) and unmet needs in patient support: Results from the International Kidney Cancer Coalition (IKCC) Global Patient Survey (GPS).

Eric Jonasch, Axel Bex, Saeed Dabestani, Selcuk Erdem, Roman Sosnowski, Yüksel Ürün, Deborah Ann Maskens, Margaret M. Hickey, Christine Collins, Karin Kastrati, Michael A.S. Jewett; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Royal Free London NHS Foundation Trust, London, United Kingdom; Department of Translational Medicine, Division of Urological Cancers, Lund University, Malmö, Sweden and Department of Urology, Kristianstad Central Hospital, Region Skane, Kristianstad, Sweden; Division of Urologic Oncology, Department of Urology, Istanbul University Faculty of Medicine, Istanbul, Turkey; Department of Urology and Oncological Urology, Warmian-Masurian Cancer Center, Olsztyn, Poland; Ankara University School of Medicine, Department of Medical Oncology; Ankara University Cancer Institute, Ankara, Turkey; International Kidney Cancer Coalition, Utrecht, Netherlands; Kidney Cancer Canada, Mississauga, ON, Canada; Nierenkrebs-Netzwerk Deutschland E.V., Wölferstheim, Germany; Princess Margaret Cancer Centre and Department of Surgery (Urology), University of Toronto, Toronto, ON, Canada

Background: KC negatively impacts the emotional well-being of patients, and patient support services are a critical component of care to improve emotional health and patient outcomes. Since 2018, the IKCC and its network have conducted a biennial GPS to assess patient/caregiver experiences on KC burden, diagnosis, and management, determine unmet needs and country variances, and identify opportunities to close gaps. We present global data from the 2025 GPS on emotional well-being and use of patient support resources. **Methods:** An IKCC steering committee of patient advocates, medical experts and the Picker Institute (UK) designed the 2025 GPS targeting KC patients and caregivers. It was cognitively tested, translated into 16 languages, and hosted online and on paper. Data were independently analyzed using cross-tabulations. **Results:** Between Sept 24 and Nov 15, 2024, 2677 responses were received from patients (n=2049) and caregivers (n=628) from 46 countries. Globally, 85% of respondents were impacted emotionally due to KC, with impacts observed across all disease stages. The most common were disease-related anxiety (50%), fear of recurrence (49%), sadness/depression (36%), and fear of dying (35%). Respondents aged 80+ and 66–80 years reported fewer emotional concerns than younger respondents. Globally, only 40%–66% of respondents discussed emotional concerns with a healthcare provider (HCP). Respondents from India and Mexico were more likely to discuss concerns with an HCP, while those from the Republic of Korea were least likely to discuss concerns. Many conversations with HCPs were considered unhelpful; notably, 33% indicated discussions about difficulties navigating the healthcare system were unhelpful. Globally, 50% of respondents accessed a patient support group, either in person or online. Respondents from Japan (19%), Türkiye (24%), France (25%), and Italy (27%) were least likely to access a patient support group, while those from India (90%) and the Republic of Korea (88%) were most likely to access a group. Overall, 47% said support groups were helpful. Patient organization websites (28%) and online support groups (27%) were considered most helpful, with variations observed across countries. Respondents indicated a desire for more counselling and/or psychological support, in-person support, peer-to-peer support, and online support. **Conclusions:** Most respondents experienced an impact on their emotional well-being due to KC; however, many did not discuss their emotional concerns with an HCP or access a patient support group either in person or online. Improved communication is needed between patients/caregivers and HCPs to address emotional concerns. HCPs can improve patient well-being through referrals to counselling/psychological support, and patient organizations in their country. Research Sponsor: None.

Efficacy with fruquintinib plus sintilimab versus axitinib or everolimus in advanced renal cell carcinoma: A post-hoc analysis from FRUSICA-2 trial by baseline tumor burden.

Yuan-Yuan Qu, Zhisong He, Xiaodong Zhang, Xin Yao, Yu Xie, Jianming Guo, Jing Li, Bin Hu, Jiasheng Bian, Chaochao Liang, Jun Xiao, Nian-Zeng Xing, Lulin Ma, Xiaoping Zhang, Zhenhua Liu, Hui Chen, Qing Zou, Chuize Kong, Songhua Fan, Dingwei Ye; Fudan University Shanghai Cancer Center, Shanghai, China; The First Hospital of Peking University, Beijing, China; Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Hunan Cancer Hospital, Changsha, China; Zhongshan Hospital, Fudan University, Shanghai, China; Henan Cancer Hospital, Zhengzhou, China; Department of Urology, Liaoning Cancer Hospital & Institute, Shenyang, China; Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China; The First Affiliated Hospital of Anhui Medical University, Hefei, China; The First Affiliated Hospital of USTC Anhui Provincial Hospital, Hefei, China; Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Peking University Third Hospital, Beijing, China; Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China; West China Hospital of Sichuan University, Chengdu, China; Harbin Medical University Cancer Hospital, Harbin, China; Jiangsu Cancer Hospital, Nanjing, China; The First Hospital of China Medical University, Shenyang, China; HUTCHMED, Shanghai, China

Background: The multicenter randomized phase 2/3 FRUSICA-2 trial (NCT05522231) demonstrated that fruquintinib plus sintilimab (F+S) significantly improved progression-free survival (PFS) (22.2 months vs 6.9 months) and objective response rate (ORR) (60.5% vs 24.3%) by blinded independent central review (BIRC) assessment compared to axitinib or everolimus (A/E) in Chinese patients (pts) with advanced renal cell carcinoma (aRCC) who had failed prior tyrosine kinase inhibitor therapy (Ye D, et al; 2025 ESMO). Considering that baseline tumor burden may correlate with efficacy outcome, we present the results of a relevant *post-hoc* subgroup analysis. **Methods:** Overall, 234 eligible pts were 1:1 randomized to receive either F+S or A/E. The primary efficacy endpoint was PFS assessed by BIRC per RECIST 1.1; secondary endpoints included investigator-assessed PFS, ORR, disease control rate, duration of response, time to response, and overall survival. This subgroup analysis evaluated BIRC-assessed PFS and ORR across subgroups defined by the number of target lesions (TLs) and metastatic sites (METs) at baseline. **Results:** At baseline, 79, 79, 32 and 44 pts had 1, 2, 3 and ≥ 4 TL(s), respectively. Metastatic disease was present in 117 (98.3%) pts in F+S arm and 110 (95.7%) pts in A/E arm, with a higher proportion of pts in F+S arm (88, 73.9%) having ≥ 3 METs than in A/E arm (67, 58.3%). By the data cut-off date of Feb 17, 2025, median follow-up for PFS was 16.6 months. As summarized in the table, F+S demonstrated superior PFS versus A/E across all subgroups, with unstratified hazard ratios (HRs) ranged from 0.28 to 0.50, as well as consistently longer median PFS. Similarly, improvements in ORR were observed across subgroups with odds ratios (ORs) ranged 2.46~7.22. Notably, in F+ S arm, fewer baseline TLs and METs appeared to correlate with longer median PFS, though such trend was not observed for ORR. **Conclusions:** Consistent with the primary analysis, F+S showed superior efficacy compared to A/E in terms of PFS and ORR in the second-line treatment of aRCC, regardless of the amount of baseline TLs or METs. Clinical trial information: NCT05522231. Research Sponsor: HUTCHMED.

Subgroup (F+S v A/E)	1 TL (38 v 41)	2 TLs (38 v 41)	3 TLs (16 v 16)	≥ 4 TLs (27 v 17)	1 MET (29 v 43)	2 METs (39 v 28)	≥ 3 METs (49 v 39)
PFS, HR (95% CI) ^a	0.39 (0.20, 0.76)	0.33 (0.17, 0.66)	0.43 (0.17, 1.10)	0.28 (0.12, 0.62)	0.28 (0.13, 0.60)	0.50 (0.24, 1.04)	0.31 (0.18, 0.545)
Median PFS, months ^b	24.9 vs 8.3	22.2 vs 6.9	15.3 vs 4.2	13.8 vs 6.9	24.9 vs 8.3	22.2 vs 8.3	NE vs 4.2
ORR, OR (95% CI) ^c	3.95 (1.35, 11.91)	4.65 (1.63, 13.43)	7.22 (1.17, 52.78)	5.53 (1.21, 28.76)	7.18 (2.22, 23.84)	2.46 (0.81, 7.76)	6.12 (2.13, 18.44)
ORR, %	52.6 vs 22.0	65.8 vs 29.3	62.5 vs 18.8	63.0 vs 23.5	65.5 vs 20.9	53.8 vs 32.1	61.2 vs 20.5

NE, not estimable.
^aBased on an unstratified Cox proportional risk model.
^bEstimated using Kaplan-Meier method.
^cExact 95% CI for OR was calculated using Cochran-Mantel-Haenszel method.

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

Neil J. Shah, Manojkumar Bupathi, Rana R. McKay, Benjamin Garnezy, Hamid Enamekhoo, Edward Paul Gelmann, Joel Picus, Brendan D. Curti, Robert A. Figlin, Hans J. Hammers, Elaine T. Lam, Pedro C. Barata, Thomas E. Hutson, Moshe C. Ornstein, Brian H. Rank, Mohamad Adham Salkeni, Song Zhao, Michael Jon Chisamore, Nandita Bose, Robert J. Motzer; Memorial Sloan Kettering Cancer Center, New York, NY; Rocky Mountain Cancer Centers, Littleton, CO; University of California San Diego, La Jolla, CA; Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN; University of Wisconsin-Madison, Madison, WI; Department of Medicine, University of Arizona, Tucson, AZ; Washington University in St. Louis, St. Louis, MO; Providence Cancer Institute, Franz Clinic, Portland, OR; Cedars-Sinai Medical Center, Los Angeles, CA; UT Southwestern Medical Center, Dallas, TX; University of Colorado Cancer Center, Aurora, CO; University Hospitals Seidman Cancer Center, Cleveland, OH; Texas Tech University Health Science Center School of Medicine, Lubbock, TX; Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; HealthPartners, Minneapolis, MN; Virginia Cancer Specialists, Fairfax, VA; Swedish Cancer Institute, Seattle, WA; Department of Clinical Development, Merck & Co., Inc., Rahway, NJ; HiberCell, Inc., Roseville, MN

Background: HC-7366 is a novel, selective, potent activator of general control nonderepressible 2 (GCN2) kinase, regulating metabolic stress via the integrated stress response. Our preclinical studies in RCC demonstrated that prolonged GCN2 activation by HC-7366 resulted in antitumor activity accompanied by inhibition of HIFs and cell cycle progression. Furthermore, combination with belzutifan (BEL) results in superior preclinical efficacy, accompanied by inhibition of HIF signaling and cell-cycle progression, supporting clinical evaluation of the combination in RCC. **Methods:** Patients with advanced ccRCC previously treated with ≥ 1 anti-PD/PD-L1 and ≥ 1 VEGF-TKI were enrolled into HC-7366 monotherapy (60 mg QD) or a dose-escalation/expansion cohort of HC-7366 (20, 40, 60 mg QD) with BEL (120 mg QD). Primary objectives were safety, tolerability, and investigator-assessed ORR per RECIST v1.1. Enrollment in escalation and expansion is complete; second expansion is ongoing. **Results:** As of the data cutoff 10 Dec 2025, 69 patients received study treatment: 16 monotherapy and 53 combination (7 at 20 mg, 22 at 40 mg, 24 at 60 mg). Median prior therapies were 3 (range 1–5) in monotherapy and 2 (range 1–4) in combination. Most TEAEs were Grade (Gr) 1–2. Gr 3 events were mainly hematological (anemia) and gastrointestinal (nausea and diarrhea), with one DLT (Gr 3 nausea, 40 mg combination). In efficacy-evaluable patients, the 40 mg combination demonstrated the best overall response rate (BORR) of 36.8%, including a confirmed ORR (cORR) of 26.3%, disease control rate (DCR) of 89.5%, and primary progressive disease (PD) rate of 10.5%. The 60 mg combination had a BORR of 31.6%, with a cORR of 31.6%, DCR of 84.2%, and primary PD rate of 15.8%. In monotherapy, BORR of 15.4% and DCR of 61.5% were observed. Early efficacy signals at 40–60 mg align with the preclinical projected maximal efficacious dose range. **Conclusions:** HC-7366, alone or in combination with BEL, was generally well tolerated. Preliminary efficacy analyses indicate favorable disease control, characterized by a high DCR and low primary PD. Clinical trial information: NCT06234605. Research Sponsor: None.

Efficacy and safety data by cohort.

	Monotherapy 60 mg N=13	HC-7366 + BELZ 20/120 mg N=7	HC-7366 + BELZ 40/120 mg N=19	HC-7366 + BELZ 60/120 mg N=19
Median follow-up (mo)	16.9	13.4	11.2	8.5
BORR / cORR (%)	2 (15.4) / 0*	0 / 0	7 (36.8) / 5 (26.3)	6 (31.6) / 6 (31.6)
DCR (%)	8 (61.5)	5 (71.4)	17 (89.5)	16 (84.2)
Primary PD (%)	5 (38.5)	2 (28.6)	2 (10.5)	3 (15.8)
PFS 6 mo (%)	15.4	42.9	57.9	73.7
Any Gr /	15 (93.8) /	7 (100) /	22 (100) /	24 (100) /
Gr 3 AEs	9 (56.3)	4 (57.1)	16 (72.7)	17 (70.8)
Gr 3 Anemia /	0 /	2 (28.6) /	5 (22.7) /	5 (20.8) /
Hypoxia	2 (12.5)	1 (14.3)	2 (9.1)	2 (8.3)
Gr 3 Nausea /	2 (12.5) /	0 /	1 (4.5) /	2 (8.3) /
Diarrhea	3 (18.8)	1 (14.3)	0	0
Dose Red /	6 (37.5) /	1 (14.3) /	11 (50.0) /	7 (29.2) /
Discont.	2 (12.5)	0	2 (9.1)	3 (12.5)

*PRs not confirmed due to emergence of brain metastases.

Combining HC-7366 with belzutifan in patients with renal cell carcinoma to alter tumor and microenvironment: Pharmacokinetic and pharmacodynamic (PK/PD) analysis of a phase 1b study.

Benjamin Garnezy, Hamid Enamekhoo, Edward Paul Gelmann, Moshe C. Ornstein, Robert A. Figlin, Manojkumar Bupathi, Brendan D. Curti, Neil J. Shah, Hans J. Hammers, C. Lance Cowey, David Aaron Schoenfeld, Scott S. Tykodi, Thomas E. Hutson, Eric Lightcap, Jeremy Drees, Weiyu Zhang, Ben Harrison, Nandita Bose, Robert J. Motzer, Rana R. McKay; Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN; University of Wisconsin-Madison, Madison, WI; Department of Medicine, University of Arizona, Tucson, AZ; Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Cedars-Sinai Medical Center, Los Angeles, CA; Rocky Mountain Cancer Centers, Littleton, CO; Providence Portland Medical Center, Portland, OR; Memorial Sloan Kettering Cancer Center, New York, NY; UT Southwestern Medical Center, Dallas, TX; Texas Oncology-Baylor Charles A. Sammons Cancer Center, The US Oncology Network, Dallas, TX; Department of Medical Oncology, Yale School of Medicine, New Haven, CT; University of Washington Medical Center, Seattle, WA; Texas Tech University Health Science Center School of Medicine, Lubbock, TX; HiberCell, Inc., Roseville, MN; University of California San Diego, La Jolla, CA

Background: Clear cell renal cell carcinoma (ccRCC), characterized by loss of von Hippel-Lindau (VHL) tumor suppressor function, and constitutive stabilization of hypoxia-inducible factor (HIF) proteins results in activation of genes promoting angiogenesis, metabolic reprogramming including altered lipid metabolism and glycolysis, cell proliferation, and immunosuppressive remodeling of the tumor microenvironment. HC-7366 is a novel, selective GCN2 kinase activator that regulates metabolic stress via the ATF4-driven integrated stress response. Preclinically, GCN2 hyperactivation with HC-7366 enhances belzutifan (BEL) activity, broadly impairing stress adaptation, disrupting tumor metabolism, decreasing HIF expression, inhibiting the cell cycle, and remodeling the tumor immune microenvironment. **Methods:** In this phase 1b study (NCT06234605), 69 patients with advanced ccRCC received HC-7366 monotherapy (60 mg QD; n=16) or HC-7366 (20 mg, n=7; 40 mg, n=22; 60 mg, n=24) plus BEL (120 mg QD). Blood samples for soluble biomarkers and paired biopsies for IHC were collected per IRB-approved guidelines. **Results:** Overall, PK analysis (N=69) demonstrated steady state free exposure of HC-7366 at 40–60 mg doses (C_{max} = 5.8 ng/mL, AUC = 75 h*ng/mL) that were consistent with exposures providing maximal BEL combination benefit preclinically. Compared with screening biopsies, all on-treatment biopsies at week 3 (8/8) showed induction of the ATF4 pathway biomarker ASNS (asparagine synthetase). Baseline HIF expression analysis by IHC from 52 patients demonstrated that 33 patients (63%) express mid to high levels of HIF1 and HIF2. HIF1 α , but not HIF2 α , was reduced consistently with treatment across all cohorts (7/8, 66–98% reduction). Reduced cell cycle biomarkers, including pRB and Ki67 (4/4), and increased frequency of CD8⁺ PD1⁺ TCF1⁺ Lag3⁻ Tim3⁻ T-cells (3/3), suggesting ICI responsiveness, were observed in the 40–60 mg combination cohorts. Systemic changes were also observed in serum, including deep and sustained inhibition of EPO, decreases in proangiogenic cytokines like VEGF-A and PDGF-BB, and changes in adipokines that counter RCC progression (Table 1). Low baseline serum levels of KIM-1 predicted response to the combination (p=0.005). **Conclusions:** Early clinical findings suggest HC-7366 + BEL is associated with modulation of angiogenic and immune-related pathways in ccRCC, providing a rationale for the combination with ICIs and/or VEGFR-TKIs. Clinical trial information: NCT06234605. Research Sponsor: None.

Avg max change with treatment.				
Biomarker	60 mg mono	20 mg combo	40 mg combo	60 mg combo
EPO (week 2)	-43%	-82%	-81%	-84%
Chemerin (week 2)	-34%	-16%	-36%	-28%
Adiponectin (week 5)	+64%	+35%	+46%	+36%
VEGF-A (week 9)	-53%	-42%	-28%	-37%
PDGF-BB (week 9)	-30%	-20%	-54%	-63%

Neoadjuvant apatinib plus camrelizumab in renal cell carcinoma with inferior vena cava tumor thrombus: Results of a phase II study.

RuiYang Xie, Ye Yan, Liyuan Ge, Zhanyi Zhang, Fan Zhang, Huiying He, Shudong Zhang; Department of Urology, Peking University Third Hospital, Beijing, China; Department of Pathology, Peking University Third Hospital, Beijing, China

Background: Renal cell carcinoma (RCC) with inferior vena cava tumor thrombus (IVCTT) remains a surgically challenging condition, and evidence supporting neoadjuvant systemic therapy is still evolving. We conducted a phase II study to evaluate the efficacy and safety of apatinib combined with camrelizumab as neoadjuvant treatment in this population. **Methods:** This single-arm phase II trial enrolled patients with histologically confirmed, resectable RCC with IVCTT (cT3b-T4, N0-1, M0-1; ECOG performance status 0-1). Patients received camrelizumab 200 mg i.v. every 2 weeks for six cycles plus oral apatinib 250 mg once daily, followed by surgical resection when feasible. The primary endpoint was downgrading of Mayo level of tumor thrombus (TT). Secondary endpoints included TT response (RECIST 1.1), response of primary renal tumor, safety (CTCAE v5.0), progression-free survival, and overall survival. **Results:** Nine patients were included in the intention-to-treat analysis. TT response was observed in 4 patients (44.4%), with disease control achieved in 8 patients (88.9%); one patient (11.1%) experienced progression. Mayo level downgrading occurred in 3 patients (33.3%), all of whom subsequently underwent surgery. Overall, 7 of 9 patients (77.8%) successfully completed neoadjuvant therapy and underwent robotic-assisted radical nephrectomy with thrombectomy. For primary renal tumor, partial response was observed in 1 patient (11.1%), and stable disease in 8 patients (88.9%), resulting in a disease control rate of 100%. Treatment-related adverse events were manageable and consistent with known safety profiles, with grade ≥ 3 events including hypertension, proteinuria, pneumonitis, and immune-related myasthenia gravis. At a median follow-up of 45 weeks, survival outcomes remain immature. **Conclusions:** Neoadjuvant apatinib plus camrelizumab demonstrated promising antitumor activity and acceptable safety in patients with RCC and IVCTT, achieving meaningful TT response and Mayo level downgrading, thereby facilitating surgical resection. These findings support further investigation of neoadjuvant combination therapy in this high-risk population. Clinical trial information: ChiCTR2300069990. Research Sponsor: National Natural Science Foundation of China; 82504235; Natural Science Foundation of Beijing Municipality; 7254443.

Patient baseline characteristics.

Characteristic	N=9
Median age, years, (IQR)	58 (54-66)
Sex, n (%)	
Male	6 (67)
Female	3 (33)
ECOG PS, n (%)	
0	7 (78)
1	2 (22)
Clinical T stage, n (%)	
cT3b	2 (22)
cT3c	3 (33)
cT4	4 (44)
Clinical N stage, n (%)	
cN0	3 (33)
cN1	6 (67)
Clinical M stage, n (%)	
cM0	3 (33)
cM1	6 (67)
Primary tumor size, cm (IQR)	12.4 (7.3-17.3)
Length of the tumor thrombus, cm (IQR)	11.3 (7.2-13.8)
Histological subtype on baseline biopsy, n (%)	
Clear cell RCC	8 (89)
TFE3 translocation RCC	1 (11)
Mayo level of TT at baseline	
I	0
II	4 (44)
III	2 (22)
IV	3 (33)

IQR interquartile range, ECOG Eastern Cooperative Oncology Group, PS performance status, RCC renal cell carcinoma.

[⁶⁸Ga] Ga-NYM096 PET/CT in patients with primary and metastatic clear cell renal cell carcinoma: A preliminary study.

Yangyang Xue, Wenjing Yu, Tao Wu, Pengfei Dai, Wei Miao, Jialun Luo, Jiaqing Huang, Si Yang, Waisi Eng, Peng Fang, P. David Mozley, Hongwei Si; Department of Nuclear Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei, China; Norroy Bioscience Co., Ltd, Wuxi, China

Background: With limitations of conventional imaging and biopsy, accurate, non-invasive techniques to detect in patients with primary and metastatic clear cell renal cell carcinoma (ccRCC) remain an unmet need. Carbonic anhydrase IX (CAIX) is a tumour antigen highly expressed in ccRCC. NYM096 is a new-generation CAIX targeting small molecule that can be labeled with ⁶⁸Ga. It has a higher affinity (almost 100-fold) for CAIX compared to NYM005. This study aims to assess the efficacy of [⁶⁸Ga]Ga-NY096 PET/CT to identify ccRCC. **Methods:** This is an open-label, multicenter study. Patients with primary and metastatic ccRCC were prospectively recruited in the study. A wash-out of 7 days was required if the patients were on tyrosine kinase inhibitors. All patients received an intravenous injection of [⁶⁸Ga]Ga-NYM096 at a dose of 1–7 mCi and underwent whole body PET/CT scan using a total-body PET/CT scanner at 60 min after injection. They were further divided into two groups: group 1, patients with primary renal mass and group 2, patients with suspected/confirmed metastatic ccRCC, who were scheduled for surgery or biopsy. In some patients, ¹⁸F-FDG PET/CT was also performed within one week before or after [⁶⁸Ga]Ga-NYM096 PET/CT. The diagnostic efficacy of ⁶⁸Ga-NYM096 was compared with that of ¹⁸F-FDG. **Results:** A total of 24 patients (mean age, 56.7 years ± 14.4, 18 men) were recruited in this preliminary study. Including 23 patients in group 1 and 1 patient in group 2. All patients had ⁶⁸Ga-NYM096 PET/CT, and all patients also had ¹⁸F-FDG PET/CT. The patient-level sensitivity, specificity, and accuracy of [⁶⁸Ga]Ga-NY096 PET scan was 100%, 90.0%, 95.7% for all patients, and 100%, 90.0%, 95.5% for group 1. One patient in Group 2 was confirmed as a true positive case by histopathological examination. Among patients with positive PET findings, the SUV_{max} of the single most active lesion ranged from 4.9 to 111.8, with a mean (± SD) of 52.2 ± 34.1. This value was significantly higher than the mean SUV_{max} of 5.5 ± 2.9 observed with ¹⁸F-FDG ($p < 0.001$). The tumor-to-kidney ratio was also higher (3.3 ± 3.0 versus 1.7 ± 3.0, $p < 0.05$). **Conclusions:** ⁶⁸Ga-NYM096 PET/CT has high diagnostic efficacy for primary ccRCC patients, and its diagnostic efficacy is significantly better than that of ¹⁸F-FDG. It has the potential to become a diagnostic product for both primary and metastatic ccRCC. Research Sponsor: Norroy Bioscience Co., Ltd.

Body composition and quality of life (QOL) with lenvatinib + everolimus (len + eve) versus cabozantinib (cabo) in metastatic clear cell renal cell carcinoma (ccRCC) after PD-1 inhibitor progression: Results from the randomized phase II LenCabo trial.

Julia Moura, Jad Chahoud, William Paul Skelton IV, Ying Yuan, Amado J. Zurita, Craig A. Kovitz, Omar Alhalabi, Matthew T. Campbell, Eric Jonasch, John Kent Lin, Monica Dandona Desai, Hyunsoo Hwang, Paul Gettys Corn, Nizar M. Tannir, Pavlos Msaouel, Andrew Warren Hahn; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Genitourinary Medical Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of Virginia, Charlottesville, VA; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of General Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The LenCabo trial (NCT05012371) was the first randomized head-to-head comparison of contemporary second-line or later treatments after progression on PD-1 based immune checkpoint inhibition (ICI). Len + eve significantly improved progression-free survival (PFS). There were numerical, but not statistically significant, differences in treatment discontinuation and $\geq$ grade 3 adverse events. Although cabo and len share many kinase targets, lenvatinib also blocks FGFR, and its combination with the mTOR inhibitor everolimus may affect body composition through metabolic effects. We sought to investigate how patient QOL and body composition changed after treatment with len + eve and cabo. **Methods:** LenCabo was a multicenter, phase II trial that randomized pts with metastatic ccRCC to len 18 mg/d plus eve 5 mg/d vs cabo 60 mg/d after 1-2 prior lines of treatment, including a PD-1 ICI. Pre-planned, health-related QOL was measured by FKS DRS at baseline and after 60 days. Post-hoc, body composition was measured using an AI segmentation tool (Voronoi DAFS) at the L3 vertebra from baseline CT scans and after 4 months. Outcomes were compared using proportional odds models adjusting for baseline values and including nonlinear terms as restricted cubic splines. Pre-specified, body composition models additionally adjusted for prior VEGF-targeted therapy, age, IMDC risk category, and sex. **Results:** 86 pts received at least 1 dose of assigned len + eve (n=40) or cabo (n=46). 38 pts completed baseline and day 60 FKS DRS (len + eve = 20, cabo = 18). The QOL comparison by FKS DRS at day 60 was inconclusive (OR = 0.51 in favor of cabozantinib, 95% CI 0.16-1.64, p=0.26). 67 pts had body composition measured at baseline and 4 months (len + eve = 30, cabo = 37). After 4 months of treatment, len + eve was associated with a significantly lower odds of having a higher body mass index (BMI), skeletal muscle mass (SMMi), and subcutaneous adiposity (SATi, Table). **Conclusions:** In patients with metastatic ccRCC progressing on PD-1 ICI, len + eve was associated with significantly greater reductions in BMI, skeletal muscle mass, and subcutaneous adiposity compared with cabo at 4 months. The study did not contradict the supposition that the two treatment arms yield the same QOL at day 60. These results suggest that the superior PFS efficacy of len + eve in this setting is accompanied by a more pronounced catabolic effect. Clinical trial information: NCT05012371. Research Sponsor: Eisai.

Body composition measures at 4 months by treatment.

	Adjusted mean of len + eve vs. cabo	Odds ratio for higher measure (95% CI)	P value
BMI	28.5 vs. 29.4	0.36 (0.15 – 0.88)	0.03
SMMi	47.5 vs. 49.7	0.30 (0.11 – 0.79)	0.01
SATi	65.7 vs. 73.4	0.21 (0.08 – 0.55)	0.002

Abbreviations: BMI, body mass index; SMMi, skeletal muscle mass index; SATi, subcutaneous adipose tissue index.

Defining second-line sequencing in advanced renal cell carcinoma: A systematic review and meta-analysis.

Luisana Sisca, Mariam Grazia Polito, Alessio Cortellini, Bruno Vincenzi, Giuseppe Tonini, Francesco Pantano; Campus Bio Medico, Roma, Italy; Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Roma, RM, Italy; Imperial College London, London, United Kingdom; University Campus Bio-Medico, Rome, Italy; Department of Medical Oncology, University Campus Biomedico, Roma, Italy; Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy

Background: In the absence of head-to-head comparative trials, the optimal sequencing of second-line systemic therapy for advanced renal cell carcinoma (RCC) remains undefined. As immune checkpoint inhibitor (ICI) based regimens now represent the dominant first-line standard, second-line treatment decisions increasingly rely on indirect data. We conducted a systematic review and meta-analysis to assess the comparative clinical reliability, defined as consistency of benefit across trials, of commonly adopted second-line strategies in RCC. **Methods:** Randomized phase II–III and prospective trials evaluating second-line systemic therapies in advanced RCC were identified through a systematic literature search. 13 trials encompassing approximately 5,000 patients were included, predominantly post TKI and post immunotherapy. Treatments were grouped by mechanism of action, including tyrosine kinase inhibitor (TKI) based regimens, mTOR inhibitor based therapies, immune-based approaches, and targeted combinations. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were pooled using inverse-variance random-effects models, with heterogeneity assessed using the I^2 statistic. **Results:** TKI based strategies demonstrated the most consistent benefit across endpoints, with significant improvement in OS (pooled HR 0.77, 95% CI 0.67–0.87; $p < 0.0001$) and favorable PFS (HR 0.56, 95% CI 0.50–0.63; $p < 0.0001$). Targeted combination strategies achieved consistent PFS benefit (HR 0.66, 95% CI 0.53–0.81; $p < 0.0001$), which did not translate into OS advantage. In contrast, mTOR inhibitor based regimens were associated with modest PFS improvement but failed to demonstrate OS benefit (HR 1.13, 95% CI 0.95–1.35), while immune based approaches showed heterogeneous outcomes. To contextualize these findings within contemporary clinical practice, analyses restricted to patients previously treated with first line ICI based regimens demonstrated a consistent treatment pattern, with TKI based therapies retaining a robust PFS benefit (HR 0.57, 95% CI 0.51–0.64), while targeted combinations maintained a significant PFS improvement without a corresponding OS signal (HR 0.66, 95% CI 0.51–0.85). **Conclusions:** In the absence of head to head sequencing trials, this systematic synthesis of prospective evidence supports TKI based therapies as the most reliable reference second line strategy in advanced RCC, showing consistent benefit across both OS and PFS, including the immunotherapy first setting. In contrast, mTOR inhibitor based approaches and targeted combinations were associated with greater heterogeneity and did not demonstrate a consistent survival benefit despite improvements in PFS. These findings provide clinically actionable guidance for second-line treatment selection after ICI failure and underscore the need for prospective sequencing focused trials. Research Sponsor: None.

Relationships between clinical stage, pathological stage, and disease-free (DFS) survival in renal cell carcinoma as used to inform future neoadjuvant study design: ECOG-ACRIN EA8143 PROSPER analysis.

James Owain Jones, Se Eun Kim, Mohamad E. Allaf, Viraj A. Master, David F. McDermott, Sabina Signoretti, Axel Bex, Grant D. Stewart, James Blackmur, Nirmish Singla, Nabil Adra, Stephanie A. Berg, Dror Michaelson, Daniel Yick Chin Heng, Brian M. Shuch, Yasser Ged, Mehmet Asim Bilen, Gennady Bratslavsky, Michael A. Carducci, Naomi Balzer Haas; University of Cambridge, Cambridge, United Kingdom; Dana-Farber Cancer Institute-ECOG-ACRIN Biostatistics Center, Boston, MA; The James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, MD; Winship Cancer Institute of Emory University, Atlanta, GA; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Royal Free Hospital, London, United Kingdom; NHS Lohain, Edinburgh, United Kingdom; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Harvard Medical School, Boston, MA; Department of Medical Oncology, Arthur JE Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB, Canada; David Geffen School of Medicine, Los Angeles, CA; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; SUNY Upstate Medical University, Syracuse, NY; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA

Background: Estimating risk of renal cell cancer (RCC) relapse based only on pre-surgical data is key to future neoadjuvant trial design. The EA PROSPER phase 3 study accrued pts with clinical stage $\geq T2$ or $T_{any}N+$ RCC of any histology for nephrectomy. Pts were randomized to presurgical nivolumab (nivo) followed by primary tumor resection and 9 cycles of adjuvant nivo, or surgery alone followed by observation. We used PROSPER data to assess how baseline data informs risk. We reviewed cT to pT stage transitions, associated cT stages with outcome, and asked if size in addition to cT stage increases predictive accuracy. **Methods:** Pts with clear cell (cc) RCC were included. cT to pT concordance was assessed by TNM 8th edition. DFS analysis (time from surgery to recurrence, second primary, or any cause death) was performed; pts with no event were censored at date of last assessment. DFS analysis compared cT groups (cT1/cT2 vs cT3/cT4) in the overall eligible study population and within each study arm. A subset DFS analysis by tumor size among cT2a ($> 7-8cm$ vs $> 8-10cm$) and cT3a ($< 7cm$ vs $7-8cm$ vs $> 8cm$) was explored. Cox proportional hazards models were used, and log-rank test was reported to represent global p-value of each model. Wald test p-value was reported for individual group comparison (in assessing more than two groups). Two-sided p-values are reported, all p-values were considered significant at 0.05. **Results:** Of 819 pts randomized, 732 ccRCC pts (382 surgery only, 350 nivo + surgery) had data available. DFS was significantly different between cT1/cT2 vs. cT3/cT4 group, favoring cT1/cT2 among all pts (HR [cT1/cT2 as reference]=1.56, two-sided log-rank $p < 0.001$) and in each of the treatment arms separately (nivo + surgery arm HR=1.48, two-sided log-rank=0.04 ; surgery only arm HR=1.63, two-sided log-rank $p=0.007$). About half of cT1/T2 pts were upstaged to pT3/4, whereas $< 10\%$ of cT3a were downstaged to pT1b. Higher grade cT1/T2 were more likely to upstage (p -value < 0.001). 119 pts with cT2a and 233 pts with cT3a had tumor size data available. There was no significant DFS difference between tumor size groups in the cT2a subset. In cT3a patients, DFS analysis by tumor size showed a trend of increasing risk for 7-8cm and $> 8cm$ groups when compared to $< 7cm$ group, with a statistically significant difference comparing $> 8cm$ vs $< 7cm$ (HR=3.33, two-sided Wald $p < 0.001$) signifying worse outcome for pts if tumor size $> 8cm$. **Conclusions:** In ccRCC pts, baseline cT assessment is associated with DFS outcome. High grade cT1/2 pts risk pathological upstaging to pT3. cT3+ identifies high risk pts, with $< 10\%$ being downstaged. Pts with cT3a $> 8cm$ have a worse prognosis than patients with $< 7cm$ tumors. These findings should be accounted for in eligibility criteria and risk assessment models for neoadjuvant trials, and explored in other international datasets. Research Sponsor: ECOG-ACRIN.

Genomic and clinical correlates of belzutifan treatment in renal cell carcinoma (RCC): A retrospective analysis of 150 RCC patients.

Harshitha Reddy Dudipala, Yu-Wei Chen, Shayan S. Nazari, Andrew Elliott, Ninad Kulkarni, Rashad Nawfal, Liliana Ascione, Marc Machaalani, David F. McDermott, Sabina Signoretti, Pedro C. Barata, Brent S. Rose, Aditya Bagrodia, Neeraj Agarwal, Sumanta Kumar Pal, Toni K. Choueiri, Rana R. McKay; Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA; Caris Life Sciences, Phoenix, AZ; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Brigham and Women's Hospital, Boston, MA; Department of Medicine, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, CA; Department of Urology, University of California, San Diego, San Diego, CA; Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT; City of Hope Comprehensive Cancer Center, Duarte, CA; UC San Diego Moores Cancer Center, La Jolla, CA

Background: Belzutifan is a hypoxia-inducible factor-2 α (HIF-2 α) inhibitor approved for RCC that targets a central driver in RCC pathogenesis; however, predictive biomarkers of response remain poorly defined. **Methods:** Comprehensive DNA (592-gene panel or whole exome) and RNA (whole transcriptome) sequencing were performed by Caris Life Sciences on RCC samples. Clear cell RCC and RCC-NOS with VHL mutations were included. Belzutifan time on treatment (ToT) was derived from insurance claims, and patients were classified as responders or non-responders using the median ToT. **Results:** A total of 150 belzutifan-treated RCC tumors were included in the analysis, of which 29% were primary kidney tumors and the remainder were from metastatic sites. The study population was classified as responders (n=57) or non-responders (n=93) using a median time on treatment of 85 days (95% CI: 71–114). Baseline characteristics were similar, except responders were younger (median age 57 vs 64 years, p=0.007). Transcriptomic analysis showed similar HIF-2 α (median 7.78 vs 7.61) and CA9 (4.82 vs 4.54) expression between responders and non-responders without statistical significance. Responders showed enrichment of PTEN (15.8% vs. 3.3%, p=0.03) and PIK3R1 alterations (7.0% vs. 0.0%, p=0.04). Responders demonstrated numerically higher frequencies of PBRM1 (54.4% vs. 44.3%, p=0.46) and PIK3CA mutations (8.8% vs. 3.3%, p=0.24). Alterations in DNA damage response genes were also numerically more common among responders, including TP53 (14.0% vs. 4.9%, p=0.11) and ATM (3.5% vs. 1.6%, p=0.56), although none of these differences reached statistical significance. In contrast, non-responders exhibited numerically higher frequencies of BAP1 (18.0% vs. 8.8%, p=0.10), SETD2 (26.2% vs. 19.3%, p=0.27), and ARID1A (5.1% vs. 1.8%, p=0.30), all of which were also not statistically significant. **Conclusions:** HIF2- α RNA expression alone does not predict belzutifan response in RCC. Responders demonstrated alterations in PBRM1, PI3K/AKT/mTOR, and DNA damage response genes, while non-responders showed numerically higher frequencies of chromatin remodeling mutations including BAP1 and SETD2. Study limitation included small sample size and short follow-up. Larger datasets are required to validate these findings. Research Sponsor: None.

Early detection of kidney cancer using blood-based multi-gene mRNA profiling in a prospective clinical study.

Taigo Kato, Koji Hatano, Dharam P. Chauhan, Norio Nonomura, Rajvir Dahiya; Department of Urology, The University of Osaka Graduate School of Medicine, Osaka, Japan; Department of Urology, The University of Osaka, Graduate School of Medicine, Suita, Osaka, Japan; GeneVerify Inc, Hayward, CA; University of California at San Francisco School of Medicine (UCSF), San Francisco, CA

Background: Kidney cancer remains one of the most aggressive and lethal urological malignancies, largely due to late-stage diagnosis and reliance on invasive tissue biopsies. To address this unmet clinical need, we developed and clinically validated the blood-based, cell-free mRNA test. By quantifying circulating tumor-derived transcripts in plasma, this assay provides rapid and precise molecular insights, supporting precision screening, early diagnosis, prognostication, and treatment monitoring. **Methods:** In this prospective clinical study, we evaluated real-time expression levels of 30 kidney cancer-associated genes in plasma samples from 51 subjects, including 41 patients with suspected kidney cancer and 10 healthy controls. The primary objective was to assess the diagnostic and prognostic performance of the Geneverify multi-gene blood-based expression panel. Log₂ fold-change values for individual genes were calculated relative to healthy controls and integrated to generate a composite risk score for each subject. Geneverify scores were compared with biopsy-confirmed diagnoses to assess assay sensitivity. Additional statistical analyses evaluated correlations between Geneverify scores and tumor stage, pathological grade, and treatment status. **Results:** All biopsy-confirmed kidney cancer cases demonstrated Geneverify scores greater than 10. Using an optimized cutoff score of 10, the assay achieved 100% sensitivity for cancer detection. While healthy controls served as the baseline reference, specificity against benign or non-malignant kidney disease could not be fully assessed due to the absence of such cases in this cohort. The majority of patients had early-stage (T1a) kidney cancer. Geneverify scores showed strong correlations with tumor stage, pathological grade, and clinical status. In patients with advanced or metastatic disease undergoing systemic therapy, Geneverify scores declined significantly over time, indicating potential utility for real-time treatment response monitoring. **Conclusions:** This study represents the first real-time clinical validation of a blood-based, cell-free mRNA genomic assay for kidney cancer detection. The Geneverify test demonstrated excellent diagnostic sensitivity, strong concordance with biopsy-confirmed disease, and meaningful prognostic and treatment-monitoring capabilities. These findings establish Geneverify as a powerful non-invasive alternative to tissue biopsy (based on published data 20% biopsies are false negative) for early detection and precision management of kidney cancer, with the potential to reduce invasive procedures and accelerate personalized oncology care. Research Sponsor: None.

Comprehensive characterization of HIF-2 α and carbonic anhydrase IX expression and the genomic landscape in clear cell and *VHL*-altered renal cell carcinoma.

Yu-Wei Chen, Shayan S. Nazari, Andrew Elliott, Ninad Kulkarni, Rashad Nawfal, Liliana Ascione, Marc Machaalani, David F. McDermott, Sabina Signoretti, Pedro C. Barata, Brent S. Rose, Aditya Bagrodia, Neeraj Agarwal, Sumanta Kumar Pal, Toni K. Choueiri, Rana R. McKay; Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA; Caris Life Sciences, Phoenix, AZ; Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine and Medical Center, American University of Beirut, Beirut, Lebanon; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Brigham and Women's Hospital, Boston, MA; Department of Medicine, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, CA; Department of Urology, University of California, San Diego, San Diego, CA; Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT; City of Hope Comprehensive Cancer Center, Duarte, CA; UC San Diego Moores Cancer Center, La Jolla, CA

Background: Clear cell renal cell carcinoma (ccRCC) is commonly driven by VHL loss, resulting in HIF-2 α stabilization and upregulation of targets such as carbonic anhydrase IX (CA9). Clarifying the relationship between CA9 and HIF-2 α expression is critical to guide rational therapeutic strategies. **Methods:** DNA (592-gene panel or whole exome) and RNA (whole transcriptome) sequencing was performed on ccRCC and RCC—not otherwise specified, (NOS) tumors with *VHL* alterations via Caris Life Sciences for integrated genomic and transcriptomic profiling. The primary objective was to characterize the expression patterns of HIF-2 α and CA9 across RCC tumors and co-occurring genomic alterations. Overall survival (OS) as measured from initial diagnosis. **Results:** A total of 1,935 RCC tumors were analyzed, including 967 (50%) ccRCC and the remainder RCC—NOS with *VHL* alterations; 49% were derived from the primary site. Expression of HIF-2 α and CA9 were similar across racial and ethnic subgroups. Compared to primary kidney tumors, lower HIF-2 α expression was observed in lymph node and liver metastases (both $p < 0.0001$) and lower CA9 expressions were observed in CNS and bone metastases (both $p < 0.0001$). Increased either HIF-2 α or CA9 expressions were associated with high angiogenic and T-effector gene signatures as defined in IMmotion150 (all $p < 0.001$). HIF-2 α expression positively correlated with CA9 expression ($r=0.43$, $p < 0.001$). Tumors with highest quartile HIF-2 α expression (Q₄) had increased PBRM1 and decreased BAP1, TP53, and TERT mutation frequencies (Table). High CA9 expression (Q₄) had increased PBRM1 and decreased TP53 mutations. High HIF-2 α (Q₄) and CA9 (Q₄) expressions were associated with improved OS compared with Q₁ (HIF-2 α : median OS 97 vs 64.7 months, HR 0.56, $p < 0.0001$; CA9: median OS 90 vs 49 months, HR 0.63, $p = 0.002$). **Conclusions:** High expression of HIF-2 α and CA9 identifies a canonical VHL/HIF-driven RCC subtype marked by enrichment of PBRM1 mutations, depletion of aggressive genomic alterations (BAP1, TP53, TERT), and improved OS. Strong associations with angiogenic and immune-related gene signatures further support a coherent HIF-dependent phenotype. Research Sponsor: None.

Key gene mutation frequency by HIF-2 α /CA9 expression.

	HIF-2 α (Q1)	HIF-2 α (Q4)	P value	CA9 (Q1)	CA9 (Q4)	P value
PBRM1	33%	48%	<0.001	22%	46%	<0.001
BAP1	29%	8%	<0.001	22%	19%	0.43
TP53	13%	7%	0.012	16%	8%	0.04
TERT	13%	6%	0.005	12%	8%	0.37

A first-in-human phase 1 dose-escalation study of the oral HIF-2 α inhibitor JMKX003948 in patients with renal cell carcinoma.

Xieqiao Yan, Xinan Sheng, Zhihong Chi, Chuanliang Cui, Lu Si, Yan Kong, Bin Lian, Lili Mao, Juan Li, Huayan Xu, Xiaowen Wu, Huihui Xiang, Lina Gu, Lei Yang, Jun Guo; Peking University Cancer Hospital, Beijing, China; Shanghai Jeyou Pharmaceutical Co., Ltd., Shanghai, China

Background: Hypoxia inducible factor-2 alpha (HIF-2 α) is a transcription factor and key tumorigenic driver of clear cell renal cell carcinoma (ccRCC). JMKX003948 is a novel, orally administered, selective small-molecule HIF-2 α inhibitor that has shown significant antitumor activity in preclinical models of ccRCC. Herein, we present preliminary results from a phase 1 dose-escalation study of JMKX003948 in advanced ccRCC (NCT06321250). **Methods:** In this study, Patients with advanced ccRCC who had received at least 1 prior standard therapy were enrolled in 40, 80, 120, 180, and 270 mg escalating-dose cohorts sequentially, and received JMKX003948 monotherapy once daily (QD) until progression or unacceptable toxicity. The primary endpoints included safety/tolerability, the maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D). **Results:** As of Dec 23, 2025, 22 patients (17 male) were enrolled. Median age was 57.5 years (range, 32–73 years). 13 patients (59.1%) have received ≥ 2 prior lines of therapy, 20 patients (90.9%) have received immune checkpoint inhibitor, and all patients (100%) have received vascular endothelial growth factor receptor–tyrosine kinase inhibitor (VEGFR-TKI). At data cutoff, the median follow-up was 9.7 months. One dose-limiting toxicity (grade 3 transaminase elevation) was observed at the 120 mg QD dose level, and the MTD was not reached. Treatment-related adverse events (TRAEs) were reported in all patients, with most graded 1–2. The most common TRAEs were anemia (86.4%). Grade 3 TRAEs occurred in 6 patients (27.3%), including hypoxia (13.6%), anemia (9.1%), proteinuria (4.5%), transaminase elevation (4.5%), and hyperkalemia (4.5%). No grade 4 TRAEs occurred. No TRAEs led to treatment discontinuation or death. Of 20 efficacy-evaluable patients, 5 patients (2 patients in 270 mg cohort and 1 patient each in 80, 120, 180 mg cohort) had partial response (PR), and 9 patients had stable disease (SD), objective response rate (ORR) and disease control rate (DCR) per RECIST 1.1 were 25% and 70%, respectively. Mean time to response (TTR) was 3.2 months. Median progression-free survival (PFS) was 7.7 months (95% CI, 1.3–not available). **Conclusions:** JMKX003948 is well tolerated and shows promising antitumor activity in patients with advanced ccRCC. Clinical trial information: NCT06321250. Research Sponsor: Shanghai Jeyou Pharmaceutical Co., Ltd.

Investigating mechanisms of resistance to immune checkpoint inhibitors (ICIs) in renal cell carcinoma (RCC).

Soki Kashima, David A. Braun, Rishabh Rout, Zhaochen Ye, Colin Laughlin, Nicholas R. Schindler, Ro Malik, Maxine Sun, Gwo-Shu Mary Lee, Wenxin Xu, Sabina Signoretti, Michael E. Hurwitz, Adebowale Adeniran, Peter Humphrey, Patrick Aloysius Kenney, Bradley Alexander McGregor, Rana R. McKay, Lu Gan, Stephen DeWall, Toni K. Choueiri; Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; 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; Department of Medicine and Urology, University of California San Diego, La Jolla, CA; Scholar Rock Inc., Cambridge, MA; Scholar Rock, Cambridge, MA

Background: Though RCC often exhibits substantial CD8 T-cell infiltration, CD8 abundance does not predict clinical benefit from ICIs. We sought to elucidate tumor microenvironment features that uncouple CD8 presence from ICI response and to evaluate strategies to overcome resistance mechanisms. **Methods:** We performed single-cell RNA sequencing on 70 RCC tumors (59 clear-cell; 11 non-clear-cell), including samples obtained during systemic therapy (ICI-based therapy, n = 46; others, n = 24). Best response to ICI-based therapy was assessed according to RECIST: 18 responders (R; CR/PR) and 11 non-responders (NR; PD). Tumor-reactive TCRs were inferred using VDJdive. Non-negative matrix factorization identified gene programs associated with NR. Bulk RNA-seq data from landmark clinical trials (HCRN, JAVELIN Renal 101, CheckMate 9ER, COSMIC-313) were analyzed using Scissor (Sun et al. Nat Biotechnol 2022) to map PFS-associated bulk signals to single-cell states in our reference dataset, with summarized enrichment as an observed-to-expected (O/E) ratio. Ligand-receptor (NicheNet) and pathway analyses implicated upstream drivers. Functional validation was performed using primary human T cells cultured under normoxia or hypoxia, with or without TGFβ1. A TGFβ activation assay was used to evaluate rescue of T-cell function by the clinical-stage latent TGFβ1-selective inhibitor SRK-181. **Results:** We profiled 443,337 high-quality cells including 86,865 CD8 T cells. In NR tumors, a subset with high tumor-specific T-cell abundance (5/11, 45.5%) was enriched for an exhausted CD8 state with a tissue-resident memory program (Tex-rm; p < 0.01). Across multiple ICI-treated clinical trial cohorts, we identified Tex-rm cells as most associated with shorter PFS (O/E 1.34–1.82). Ligand-receptor and pathway analyses implicated enhanced TGFβ signaling in Tex-rm compared with other Tex. In vitro, hypoxia plus TGFβ1 increased a Tex-rm-like phenotype (CD69⁺CD103⁺PD-1⁺TIM-3⁺) relative to controls (p < 0.05 for each). TGFβ inhibited T-cell IFNγ production, while treatment with the TGFβ inhibitor SRK-181 restored it (p < 0.05). **Conclusions:** We identified a Tex-rm program associated with ICI intrinsic resistance in RCC despite high abundance of tumor-specific T cells. Functional data support a role for TGFβ signaling in promoting this dysfunctional state, suggesting that inhibiting TGFβ1 may help restore T-cell function and overcome ICI resistance in some non-responders. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Biomarker-defined outcomes in metastatic clear cell renal cell carcinoma (mccRCC) receiving first-line (1L) immune checkpoint inhibitor-based therapy.

Koral U. Shah, Jennifer Rider, Ryan Pindale, Miguel Zugman, Salvador Jaime-Casas, Vitor Abreu De Goes, Ali Moradi, Nicholas Salgia, Peter D. Zang, Daniela V. Castro, Benjamin Mercier, George Zhang, Yujun Li, Nazli Dizman, Joann Hsu, Wesley Yip, Abhishek Tripathi, Charles B. Nguyen, Alex Chehrazi-Raffle, Sumanta Kumar Pal; City of Hope Comprehensive Cancer Center, Duarte, CA; ConcertAI, LLC, Cambridge, MA; ConcertAI, Cambridge, MA; Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Dual immune checkpoint inhibitor (IO-IO) and immune checkpoint inhibitor plus VEGF receptor tyrosine kinase inhibitor (IO-TKI) regimens are approved 1L treatments for mccRCC, yet treatment selection remains empiric in the absence of prospective comparisons and validated predictive biomarkers. While prior retrospective studies have linked genomic alterations such as *PBRM1* with favorable immunotherapy outcomes (Miao et al., 2018), the impact of these alterations across IO-IO vs. IO-TKI regimens is not well characterized. We evaluate PD-L1 expression and tumor genomic alterations in relation to clinical outcomes among patients receiving 1L IO-based therapy. **Methods:** Adults with mccRCC diagnosed through 2/4/2025 were identified in ConcertAI's Patient360, a U.S. de-identified database integrating health records, claims, genomics, and mortality data. Patients initiating 1L IO-IO (ipilimumab + nivolumab) or IO-TKI (cabozantinib + nivolumab, pembrolizumab + axitinib, or lenvatinib + pembrolizumab) were included. Molecular testing performed prior to or during 1L therapy was collected. PD-L1 positivity was defined as $\geq 1\%$ tumor cell staining. Overall survival (OS) and progression-free survival (PFS) were estimated via Kaplan-Meier methods; associations by treatment and biomarker status were assessed using Cox models. **Results:** Among 4,845 patients with mccRCC, 3,225 patients had 1L treatment data, of whom 1,007 (31.2%) received IO-based therapy. IO-based therapy included IO-IO (508 patients; 50.4%) and IO-TKI (499 patients; 49.6%). Among patients receiving IO-based therapy, median age was 62 years, and 63.6% had *de novo* metastatic disease. Tumor genomic alterations were identified in 125 patients, including *VHL* (77.6%), *PBRM1* (50.4%), *BAP1* (28.8%), and *SETD2* (4.8%). Patients with any alterations in *VHL*, *PBRM1*, or *BAP1* demonstrated significantly longer median PFS with IO-TKI compared with IO-IO (37.9 vs. 18.4 months, respectively; $p=0.04$). In gene-specific analyses, similarly large numerical differences in PFS were observed with IO-TKI vs. IO-IO amongst patients with *VHL* (38.0 vs. 18.4 months) and *PBRM1* (34.4 vs. 18.4 months) alterations. In the overall cohort, median PFS was 32.2 vs. 20.8 months ($p=0.06$), and median OS was 58.4 vs. 56.7 months ($p=0.60$) for IO-TKI and IO-IO, respectively. Among 102 patients with available PD-L1 status, 25.5% were PD-L1-positive and 74.5% were PD-L1-negative. Among PD-L1-positive patients, OS and PFS did not significantly differ between regimens. **Conclusions:** Among patients with mccRCC receiving 1L IO-based therapy, those harboring *VHL*, *PBRM1*, or *BAP1* alterations were collectively associated with numerically longer PFS when treated with IO-TKI. These findings represent one of the first and largest biomarker-stratified comparisons of outcomes between IO-TKI and IO-IO regimens. Research Sponsor: None.

First-line tivozanib in favorable- and very favorable-risk metastatic renal cell carcinoma: Real-world evidence from the TIVOREAL-SOGUG study.

Cristina Pernaut Sanchez, Laura López, Javier Gavira, Angel Rodriguez, Begoña P. Valderrama, Alejandro Jose Barroso Martinez, Maria Jose Mendez Vidal, Rosa Maria Rodriguez-Alonso, Enrique Gallardo, Aranzazu Gonzalez del Alba, Guillermo Crespo, Lucía Oliva, Miguel A. Climent Duran, Cristina Suárez, Imanol Martinez, José Antonio Folgueira Vigo, Inmaculada Aparicio Salcedo, Victoria Tirado Anula, Sergio Vázquez Estévez, Jose Angel Arranz Arija; Hospital Universitario Severo Ochoa, Leganes, Madrid, Spain; Hospital de León, León, Spain; Institut Català d'Oncologia, L'Hospitalet De Llobregat, Barcelona, Spain; Hospital de León, León, Spain; Hospital Universitario Virgen del Rocío, Sevilla, Spain; Hospital Universitario Virgen del Rocío, Sevilla, Spain; Maimonides Institute for Biomedical Research of Cordoba (IMIBIC), Hospital Universitario Reina Sofía, Medical Oncology Department, Córdoba, Spain; Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), Hospital Universitario Reina Sofía, Medical Oncology Department, Córdoba, Spain; Department of Oncology, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain, Sabadell, Spain; Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; Hospital Universitario de Burgos, Burgos, Spain; Hospital Universitario Virgen de la Victoria, Málaga, Spain; Instituto Valenciano de Oncología, Valencia, Spain; Hospital Universitario Vall d'Hebron, Barcelona, Spain; Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Hospital Universitario Lucus Augusti, Lugo, Spain; Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background: The optimal first-line treatment for favorable-risk metastatic renal cell carcinoma (mRCC) remains debated in the immune checkpoint inhibitor (ICI) era. Real-world data assessing prognostic subgroups treated with VEGFR-TKI monotherapy are limited. **Methods:** TIVOREAL-SOGUG is a retrospective multicenter study including patients with clear-cell mRCC treated with first-line tivozanib between 2017 and 2024 across 14 Spanish centers. Favorable-risk was defined by IMDC criteria (0 risk factors). A very favorable-risk (VFAV) subgroup was identified according to Zarba et al. criteria (time from diagnosis to systemic therapy >3 years, Karnofsky performance status 90–100%, and absence of brain, liver, or bone metastases). The primary endpoint was time to treatment failure (TTF); secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), subsequent therapies, and safety. **Results:** Among 198 evaluable patients, 84 (42.4%) had favorable-risk disease, including 23 (27.4%) classified as VFAV. In the overall favorable-risk cohort, ORR was 48.8%, including 7.1% complete responses. Median PFS and TTF were 23.7 and 14.7 months, respectively. Median OS was not reached, with 2- and 5-year OS rates of 85.4% and 67.8%. VFAV-risk patients showed higher ORR (65.2%), prolonged PFS (32.2 months) and TTF (31.1 months), and low primary progression. Treatment discontinuation due to toxicity occurred in 9.5% of patients. Most frequent adverse events were grade 1–2 fatigue, diarrhea, mucositis, dysphonia and hypertension, with grade ≥3 events being infrequent and mainly limited to hypertension. After progression, most favorable-risk patients received ICIs, whereas VFAV-risk patients required subsequent therapy less frequently, reflecting more durable disease control. **Conclusions:** In routine clinical practice, first-line tivozanib provides durable disease control and long-term survival in IMDC favorable-risk mRCC, and particularly in VFAV-risk patients. ICI and cabozantinib remain effective salvage options in this setting upon disease progression. Research Sponsor: Recordati Rare Diseases Spain, S.L.U.

Key clinical outcomes by prognostic subgroup.		
Outcome	Favorable-risk (n=84)	Very favorable-risk (n=23)
Median TTF, months (95% CI)	14.7 (9.2–20.1)	31.1 (8.0–54.1)
Median PFS, months (95% CI)	23.7 (14.1–33.3)	32.2 (21.1–43.4)
ORR, % (CR %)	48.8 (7.1)	65.2 (13.0)
Primary progressive disease, %	14.3	4.3
2-year OS, % (95% CI)	85.4 (77.2–92.8)	95.7 (88.1–100)
Discontinuation due to toxicity, %	9.5	8.7

TTF and PFS were estimated using Kaplan–Meier methodology; tumor response was assessed according to RECIST 1.1.

LIF expression as a predictive biomarker in metastatic renal cell carcinoma.

Mustafa Saleh, Eddy Saad, Marc Machaalani, Kevin Meli, Jad El Masri, Ro Malik, Harry Kane, Renee Maria Saliby, Chris Labaki, Tarek Baroud, Pablo Barrios, Liliana Ascione, Wassim Daoud Khatoun, Emre Yekeduz, Sabina Signoretti, Alexander Gusev, Eliezer Mendel Van Allen, David A. Braun, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; Brigham and Women's Hospital, Boston, MA

Background: Clear cell renal cell carcinoma (ccRCC) is biologically heterogeneous, and optimal selection between VEGF-targeted and ICI-based therapies remain an unmet clinical need. Leukemia inhibitory factor (LIF), an IL-6 family cytokine implicated in angiogenesis and immune regulation, is associated with poor prognosis in ccRCC; however, its predictive value for treatment selection has not been defined. **Methods:** Baseline tumor LIF expression was evaluated in 2,026 patients with metastatic ccRCC across 12 clinical and molecular cohorts, including CheckMate 009/010/025/214, JAVELIN Renal 101, IMmotion150, TCGA-KIRC, CPTAC-3, and institutional datasets. RNA-seq data were batch-corrected, normalized, and immune-deconvoluted (CIBERSORTx). Among 1,306 patients with treatment data, 1,058 with complete clinical covariates were included in treatment-by-biomarker interaction analyses. **Results:** LIF-high tumors (median cutoff) were associated with younger age (60 vs 63 years, $p<0.001$) and increased sarcomatoid features (17% vs 8%, $p<0.001$). A significant treatment-by-LIF interaction was observed for progression-free survival (PFS; interaction $p=0.006$). High LIF expression predicted inferior PFS on TKI monotherapy (HR 1.26, $p<0.001$), while this adverse association was absent with ICI-based regimens (monotherapy or combination; HR 0.70, $p<0.001$). No significant interaction was observed for overall survival. LIF expression discriminated progressive disease from disease control ($p<0.001$). Immune deconvolution revealed that LIF-high tumors exhibited an inflamed but immunosuppressive microenvironment, characterized by enrichment of macrophages (M0 and M2), neutrophils, and regulatory T cells, with preserved CD8⁺ T-cell infiltration. LIF expression correlated strongly with CXCL8 ($R=0.45$), and more modestly with FGF2 and VEGFA, consistent with VEGF-independent angiogenic signaling. **Conclusions:** LIF identifies a biologically distinct subset of metastatic ccRCC characterized by angiogenic and immunosuppressive features and poor outcomes with TKI monotherapy. These data support LIF as a predictive biomarker to inform treatment selection and highlight the LIF/CXCL8 axis as a potential therapeutic target in advanced RCC. Research Sponsor: None.

Treatment-by-LIF interaction analysis for progression-free survival in metastatic clear cell renal cell carcinoma.

Groups	N	HR	95% CI	P-value
Full Cohort*	1792	1.09	1.01 - 1.14	0.017
Treatment interaction Model [§]				
Main effect (LIF in TKI)	1058	1.26	1.108 - 1.443	<0.001
LIF × IObased (IO and IO+IO)	1058	0.70	0.567 - 0.854	<0.001
LIF × IO+VEGF	1058	0.89	0.73 - 1.079	0.230
LIF × MTORi	1058	0.84	0.689 - 1.035	0.104
Stratified Analyses [§] : TKI Monotherapy	377	1.27	1.114 - 1.455	<0.001
IO/IO+IO	194	0.87	0.741 - 1.03	0.107
IO+VEGF	364	1.15	0.996 - 1.337	0.057

*Adjusted for IMDC, Age, Sex, Sarcomatoid Features, and Treatment modality.

[§]Adjusted for IMDC, Age, Sex, Sarcomatoid Features.

Nivolumab and Ipilimumab (NIVO IPI) as first-line (1L) treatment for patients with metastatic renal-cell carcinoma (mRCC): A real-world benchmarking analysis from the International mRCC Database Consortium (IMDC).

Heber Tomas Reyes-Garcia, Elio Ibrahim, Connor Wells, Benoit Beuselinck, Lori Wood, Jae Lyun Lee, Christian K. Kollmannsberger, Christina M. Canil, Rana R. McKay, Georg A. Bjarnason, Zeynep Irem Ozay, Frede Donskov, Thomas Powles, Ali Moradi, Parker Baumgarten, Jeremy David Shapiro, Elizabeth Chien Hern Liow, Martin Zarba, Toni K. Choueiri, Daniel Yick Chin Heng; Arthur JE Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB, Canada; Dana-Farber Cancer Institute, Boston, MA; Arthur JE Child Comprehensive Cancer Centre, Calgary, AB, Canada; University Hospital Leuven, KU Leuven, Leuven, Belgium; Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada; Asan Medical Center, Seoul, South Korea; British Columbia Cancer Agency, Vancouver, BC, Canada; The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; UC San Diego School of Medicine, San Diego, CA; Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT; University Hospital of Southern Denmark, Esbjerg, Denmark; Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, United Kingdom; City of Hope Comprehensive Cancer Center, Duarte, CA; Cabrini Haematology and Oncology Centre, Malvern, VIC, Australia; Monash Health, Victoria, Australia

Background: NIVO IPI has demonstrated durable overall survival (OS) benefit with long-term follow-up in patients with mRCC. Real world outcomes and benchmarks for subgroups as well as conditional survival (CS) are required in the real world. **Methods:** Patients with mRCC treated with 1L NIVO IPI from the IMDC were analyzed, including various subgroups of interest. Outcomes reported will be objective response rates (ORR), median overall survival (mOS) and conditional survival (CS). CS is defined as survival among patients who were alive and on treatment after the requisite 3-month interval landmarks, as estimated using the Kaplan–Meier method. CS was calculated at landmarks while patients were still on treatment, and at landmarks regardless of treatment. **Results:** 2115 patients received 1L NIVO IPI; 148/1042/549 were categorized by IMDC risk group as favorable/intermediate/poor risk; 90% of patients had clear-cell histology, 32% had bone metastases, and 14% had sarcomatoid features. Median follow-up was 34 months (m); median duration of treatment was 4.8 m, and median time to next treatment was 11.2 m. 66% of patients received second-line treatment. ORR was 39.5% (8.3% CR) with primary progression seen in 28 mOS was longer in clear cell (47.8 m) than in non-clear cell (26.3 m) ($p < 0.001$). mOS was significantly shorter in patients with sarcomatoid features (34.2 vs 47.0 m; $p = 0.02$ mOS was also different by IMDC risk group: 53.3 m for favorable, 45.7 m for intermediate and 18.8 m for poor risk patients ($p < 0.001$); and by response: 4-year was OS of 93.6% for patients with CR, 60.1% for PR, 43.6% for SD and 15.4% for patients with PD ($p < 0.001$). CS during 1L NIVO IPI is detailed in Table 1 with greater survival with each successive landmark. **Conclusions:** We provide real-world benchmark survival results for patients with mRCC treated with 1L NIVO IPI, including subgroup analysis regarding the presence of sarcomatoid features, IMDC risk group, and ORR. Conditional survival provides a key understanding of a patient's prognosis after having been on therapy or been alive for at certain time points. This is essential information for patient counselling and clinical trial design. Research Sponsor: None.

Conditional survival (CS) through time landmarks, either on treatment or regardless of treatment.

Landmark (mo)	CS on NIVO IPI (N)	CS on treatment If patient is still on therapy past landmark mo (95% CI)	CS (N) regardless of treatment continuation	CS regardless of treatment continuation If patient survived past landmark mo (95% CI)
0	1965	41.4 (37.7–45.3)	2038	40.2 (36.7–44.5)
3	1129	54.5 (49.7–67.3)	1826	44.6 (40.7–49.4)
6	822	93.0 (60.9–NR)	1626	49.2 (44.6–53.5)
9	627	93.0 (84.2–NR)	1436	53.5 (49.2–59.2)
12	483	114 (84.2–NR)	1276	56.9 (51.1–66.8)
24	210	NR (NR–NR)	805	93.0 (72.8–NR)
36	101	NR (NR–NR)	519	NR (93.0–NR)

Extended follow-up (6 years) of the phase 2 LITESPARK-004 study of belzutifan in participants with von Hippel-Lindau disease–associated neoplasms.

Ramaprasad Srinivasan, Vivek Narayan, Othon Iliopoulos, Kathryn E. Beckermann, Benjamin L. Maughan, Stephane Oudard, Tobias Else, Jodi Kathleen Maranchie, Ane Bundsbæk Bøndergaard Iversen, Jerry Cornell, Rodolfo F. Perini, Donna Vickery, W. Marston Linehan, Eric Jonasch; Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; University of Pennsylvania, Philadelphia, PA; Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA; Vanderbilt University Medical Center, Nashville, TN; University of Utah, Salt Lake City, UT; Georges Pompidou European Hospital, University of Paris Cité, Paris, France; University of Michigan, Ann Arbor, MI; University of Pittsburgh, Pittsburgh, PA; Aarhus University Hospital, Aarhus, Denmark; Merck & Co., Inc., Rahway, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Belzutifan, a potent and selective hypoxia-inducible factor 2 α inhibitor, is indicated for treatment of patients with von Hippel-Lindau (VHL) disease–associated renal cell carcinoma (RCC), CNS hemangioblastomas (HB), or pancreatic neuroendocrine tumors (pNETs) not requiring immediate surgery based on prior results from the open-label phase 2 LITESPARK-004 study (NCT03401788). We report results from LITESPARK-004 after a minimum of 6 years of follow-up. **Methods:** Participants (pts) 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 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 73.8 months (range, 72.1–82.1). As of the data cutoff date (April 1, 2025), 34 pts (56%) remained on treatment. ORR was 70% for RCC, 52% for CNS HB, and 91% for pNETs. Additional efficacy results are shown in the Table. Among 14 pts ($n = 18$ affected eyes by ophthalmic evaluation), retinal HBs in 100% (95% CI, 81–100) of eyes showed improvement. Median DOR in pts with retinal HBs was not reached (NR; 95% CI, 8.5–NR). Within 5 years prior to initiating belzutifan, 46 of 61 pts (75%) had ≥ 1 VHL-related tumor reduction procedure (surgery or radiation therapy; 43 RCC, 39 CNS HB, 12 retinal HB, 3 pNET, 2 other). Since initiating belzutifan treatment, 22 of 61 pts (36%; 14 during treatment and 8 after discontinuing treatment) underwent 25 VHL-related tumor reduction procedures (16 RCC, 3 CNS HB, 5 retinal HB, 1 pNET). Grade 3 treatment-related adverse events (TRAEs) were reported in 12 pts (20%); the most common grade 3 TRAE was anemia (11%). No grade 4 or 5 TRAEs occurred. No additional pts discontinued belzutifan due to TRAEs since the previous analysis. **Conclusions:** After 6 years of follow-up, belzutifan continues to show durable antitumor activity and a manageable safety profile in pts with VHL-associated RCC, CNS HB, and pNETs who do not require immediate surgery. These results continue to support the use of belzutifan in this patient population. Clinical trial information: NCT03401788. Research Sponsor: Funding for this study was provided by 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 = 22
ORR (95% CI), %	70 (57-81)	52 (37-66)	91 (71-99)
Best overall response, n	8 CR 35 PR 17 SD 0 PD 1 NE	7 CR 19 PR 20 SD 3 PD 1 NE	14 CR 6 PR 2 SD 0 PD 0 NE
DOR, median (range), months	NR (5.8+ to 69.1+)	NR (0.0+ to 74.3+)	NR (11.0+ to 71.8+)
48-month DOR rate	78%	84%	90%
PFS, median (95% CI), months	NR (71.5-NR)	NR (NR-NR)	NR (NR-NR)
48-month PFS rate	79%	80%	90%

Ultrasensitive circulating tumor DNA detection and molecular clearance as a prognostic and predictive marker in advanced renal cell carcinoma.

Juan Ruiz Bañobre, Helena Lombardia-Rodriguez, Bailiang Li, Yi Chen, Charles Abbott, Candela Fernandez-Reino, Yoel Z. Betancor, Silvia Diz-de Almeida, Javier Álvarez-Fernández, Natalia Fernández-Díaz, Santiago Aguin Losada, Vanesa Vaamonde-Rodriguez, Maria Emilia Fariña-Sabater, Rosa Villaverde-Viaño, Carlos Pérez-López, Silvia Margarita Garcia-Acuna, Sean Michael Boyle, Richard Chen, Urbano Anido Herranz, Rafael Lopez; Complejo Hospitalario Universitario de Santiago, Santa, Spain; University of Santiago de Compostela (USC), Santiago de Compostela, Spain; Personalis, Inc., Fremont, CA; University Clinical Hospital of Santiago de Compostela (SERGAS), Santiago de Compostela, Spain; Department of Medical Oncology, University Clinical Hospital of Santiago de Compostela (SERGAS), Santiago de Compostela, Spain; Medical Oncology Department, Complejo Hospitalario Universitario de Santiago, Santiago De Compostela, Spain; Oncology Nursery Department, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain; Oncology Nursery Department, Complejo Hospitalario Universitario de Santiago de Copmstela, Santiago De Compostela, Spain; Department of Pathology, University Clinical Hospital of Santiago de Compostela (SERGAS), Santiago de Compostela, Spain; Hospital Clinico Universitario, Santiago De Compostela, Spain

Background: Renal cell carcinoma (RCC) is characterized by exceptionally low levels of circulating tumor DNA (ctDNA), often falling below the limit of detection for conventional liquid biopsy assays. This low-shedding environment creates a significant unmet need for ultrasensitive strategies to detect molecular residual disease (MRD), improving patient stratification, and enabling longitudinal monitoring of disease evolution in a clinical setting. **Methods:** ctDNA was profiled using NeXT Personal, a tumor-informed WGS-based assay tracking up to ~1,800 patient-specific variants with a limit of detection (LOD) of ~1 part per million (PPM). Baseline and longitudinal (n = 165) plasma from 37 advanced RCC patients were analyzed. The primary analysis evaluated baseline plasma (n = 36) across clinical variables. Prognostic value for progression-free survival (PFS) and overall survival (OS) was assessed in patients treated with immunotherapy or TKIs (n = 35). **Results:** Baseline ctDNA was detected in 84% (31/37) of patients. Notably, 13% (4/31) of these detections occurred in the ultrasensitive range below 100 PPM. Baseline ctDNA PPM levels significantly correlated with IMDC risk group (median PPM: favorable 10.9, intermediate 244.2, poor 2437.0; $P=0.005$), presence of histological high-risk features (median PPM: low-risk: 40.6 vs high-risk: 1528.0; $P=0.025$) and stage at diagnosis (median PPM: I-III 35.1 vs IV 1548.3; $P=0.006$). Median ctDNA levels were significantly lower in patients with surgical site recurrence (5.5 vs. 937.2 PPM; $P=0.038$). Molecular ctDNA clearance (mCR), defined as ctDNA-negative status at any point during first-line therapy, was highly prognostic. mCR correlated significantly with best overall response ($P=0.007$), with 100% specificity for disease control; no patients with progressive disease achieved clearance. Patients not achieving mCR had dramatically worse PFS (HR=8.69; $P=0.001$) and OS (HR=4.70; $P=0.044$). Among patients with a best response of stable disease (SD) by imaging, mCR provided critical differentiation; those who cleared ctDNA had 100% PFS/OS at 2 years, whereas those who remained ctDNA-positive saw PFS drop to 0% and OS to 33% by year 1. Additionally, achievement of mCR was significantly associated with clinical disease control (PR+SD, 92.3% vs PR+SD, 50.0%; OR 12.0 [95% CI 1.32–108.8], $p=0.013$). **Conclusions:** Ultrasensitive ctDNA profiling effectively overcomes the low-shedding challenge of advanced RCC, and could provide additional prognostic clarity that complements standard-of-care imaging and IMDC risk models. mCR serves as an effective biomarker for long-term survival, identifying patients with durable responses even among those with radiographically stable disease. These findings support integrating ctDNA monitoring to guide treatment intensification or de-escalation strategies. Research Sponsor: GILEAD SCIENCES, S.L.U. – 11a Convocatoria de Becas Gilead a la Investigación Biomédica en VIH, COVID-19, Hepatitis Delta, Linfomas no Hodgkin de células B y Oncología Médica.

Impact of time-of-day of immune checkpoint inhibitor infusion on clinical outcomes in patients with metastatic renal cell carcinoma (mRCC).

Soon Khai Low, Ranveer S. Palia, Aniko Szabo, Haisam Abid, Hiba Narvel, Sherin Daniel Ampanattu, Dariusz Uczkowski, Alexandria T. Phan, Deepak Kilari; Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI; Medical College of Wisconsin, Milwaukee, WI; Division of Biostatistics, Froedtert and The Medical College of Wisconsin, Milwaukee, WI; Division of Hematology and Oncology, Milwaukee, WI

Background: Emerging evidence suggests that circadian rhythms may influence the efficacy of immune checkpoint inhibitors (ICIs) by modulating immune cell activity and T-cell trafficking. This study evaluated whether the timing of ICI administration (early vs. late) affects progression-free survival (PFS) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC). **Methods:** We conducted a single-center retrospective study of 97 patients with Stage IV mRCC treated with first-line ICIs. Patients were categorized by infusion timing: "Early" (n=68) vs. "Late" (n=29), with the cutoff defined by the median infusion time of 2:00 PM. Treatment regimens included ipilimumab/nivolumab (37%), nivolumab (36%), and pembrolizumab (27%); 23% received ICI in combination with a VEGF-targeted tyrosine kinase inhibitor. Outcomes were analyzed using Kaplan-Meier curves and multivariable Cox regression models, adjusting for age and International Metastatic RCC Database Consortium (IMDC) risk scores. **Results:** The median age was 65 years (IQR 59–71), 77% of patients were male, and 88% had clear cell histology. IMDC risk categories were intermediate (56%), poor (27%), and favorable (18%). At a median follow-up of 54.8 months, early infusion was associated with significantly improved OS (median 54 vs. 29 months; adjusted HR 1.79; 95% CI 1.02–3.12; $p = 0.041$) and PFS (median not reached; adjusted HR 3.59; 95% CI 1.27–10.20; $p = 0.016$) after adjustment for age and IMDC risk. Landmark 60-month OS was 40% vs. 31%, and PFS was 79% vs. 60% for the early vs. late groups, respectively. The incidence of any-grade immune-related adverse events (irAEs) was similar (54% in the early group vs. 52% in the late group), and poor IMDC risk remained a significant predictor of OS in the multivariable model (HR 3.09; 95% CI 1.22–7.8; $p = 0.017$). **Conclusions:** In this mRCC cohort, ICI administration before 2:00 PM was associated with significant improvements in both PFS and OS, including a nearly two-fold increase in median overall survival compared to late-afternoon administration. These findings are hypothesis-generating and suggest that the timing of immunotherapy may be an immediately actionable, high-impact variable in optimizing mRCC treatment. Prospective validation is warranted. Research Sponsor: None.

Correlation between *CARINH* expression and clinical outcomes in metastatic clear-cell renal cell carcinoma (mccRCC).

Wassim Daoud Khatoun, Eddy Saad, Jad El Masri, Mustafa Saleh, Pablo Barrios, Chris Labaki, Harry Kane, Kevin Meli, Renee Maria Saliby, Ro Malik, Razane El Hajj Chehade, Liliana Ascione, Soki Kashima, Maxine Sun, Eliezer Mendel Van Allen, David A. Braun, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; Yale New Haven Hospital, New Haven, CT

Background: *CARINH* is an interferon (IFN)-responsive long non-coding RNA that promotes *IRF1* expression and downstream IFN signaling. Higher *CARINH* expression improves outcomes in esophageal cancer through suppressed tumor growth (Huang et al, 2019). Despite the immunogenic nature of RCC, the role of *CARINH* in its immunogenicity remains unexplored. Here, we examine the role of *CARINH* in predicting progression in mccRCC patients (pts) treated with systemic therapy. **Methods:** We included pts with RNA-seq data from 2 first-line clinical trials in mccRCC: Javelin Renal-101 (JR; n = 741) and CheckMate9ER (CM9; n = 403). Transcripts per million (TPM) were log₂-transformed and scaled per 1 SD change. IMmotion150 T_{eff} and Myeloid signatures, and tumor inflammatory score (TIS) were computed as means of their log₂-transformed genes' TPMs then scaled. Multivariable (MV) Cox models assessed progression-free survival (PFS) per increase in *CARINH* expression and compared PFS for each immune signature with and without *CARINH* expression, using likelihood ratio test (LRT). Log-rank test compared PFS between high and low *CARINH* expression groups with median split. Spearman correlation associated *CARINH* expression and immune signatures. MV logistic regression estimated progression odds ratio between pts who progressed (RECIST 1.1: PD), and those who didn't (CR, PR, SD and NCR/NPD). MV analyses adjusted (adj) for age, sex, treatment arm, IMDC risk and sarcomatoid features. **Results:** In MV Cox analysis, higher *CARINH* was associated with improved PFS in both trials (JR: HR_{adj} = 0.87 - 95% CI: 0.79-0.96, p = 4.5×10⁻³; CM9: HR_{adj} = 0.82 - 95% CI: 0.73-0.93, p = 1.3×10⁻³), regardless of treatment arm (LRT p > 0.05). Log-rank test, comparing high and low expression groups, revealed longer PFS with high expression in every cohort and their arms (p < 0.05), except for sunitinib in CM9 (p = 0.18). Higher *CARINH* expression correlated positively with T_{eff} and TIS signatures (ρ = 0.51-0.54) and negatively with Myeloid signature (ρ = -0.14 to -0.10) in both trials (p < 0.05). *CARINH* expression improved PFS prediction over immune signatures in both trials (Table). Higher expression was associated with lower progression odds (JR: OR_{adj} = 0.74 - 95% CI: 0.60-0.91, p = 3.7×10⁻³; CM9: OR_{adj} = 0.68 - 95% CI: 0.47-0.98, p = 0.04), independent of arm (LRT p > 0.05). **Conclusions:** In mccRCC, higher *CARINH* expression associates with lower progression odds and improved PFS beyond that predicted by immune signatures. Translational efforts to characterize its role in mccRCC pathophysiology and clinical outcomes are ongoing. Research Sponsor: None.

MV Cox for PFS prediction by immune signature after adding *CARINH* expression.

Trial	Immune Signature	HR _{adj} (with <i>CARINH</i>)	95% CI	LRT FDR-adj p-value
JR	TIS	0.86	0.76-0.97	0.02
JR	T _{eff}	0.88	0.79-0.99	0.04
JR	Myeloid	0.87	0.80-0.96	0.02
CM9	TIS	0.84	0.72-0.97	0.02
CM9	T _{eff}	0.81	0.70-0.94	7.2×10 ⁻³
CM9	Myeloid	0.82	0.73-0.93	4.6×10 ⁻³

A multi-axis biomarker model integrating KIM-1 and MAdCAM-1 in metastatic renal cell carcinoma.

Marc Machaalani, Renee Maria Saliby, Carolina Alves Costa Silva, Eddy Saad, Clara Steiner, Caiwei Zhong, Emre Yekeduz, Xiaowen Liu, Liliana Ascione, Pablo Barrios, Ti Cai, Gwo-Shu Mary Lee, Wanling Xie, Sabina Signoretti, Maxine Sun, Laurence Zitvogel, Laurence Albiges, David F. McDermott, Wenxin Xu, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Yale New Haven Hospital, New Haven, CT; Oncoclinicas, Rio De Janeiro, Brazil; Beth Israel Deaconess Medical Center, Boston, MA; University Hospital Leipzig, Leipzig, Germany; Ankara University Faculty of Medicine, Ankara, Turkey; IEO, European Institute of Oncology IRCCS, Milano, Italy; EMD Serono Research and Development Institute, Billerica, MA; Brigham and Women's Hospital, Boston, MA; Institut Gustave Roussy, Villejuif, France; Department of Medical Oncology, Gustave Roussy, Paris Saclay University, Villejuif, France; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Kidney injury molecule-1 (KIM-1) and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) have each emerged as prognostic circulating biomarkers in metastatic renal cell carcinoma (mRCC). Whether these biomarkers capture overlapping or complementary aspects of disease biology, and whether their integration improves risk stratification, remains unclear. **Methods:** Baseline plasma KIM-1 and MAdCAM-1 levels were measured in 612 patients with previously untreated mRCC from the JAVELIN Renal 101 trial, including 323 patients treated with avelumab + axitinib and 289 with sunitinib. Biomarker concentrations were analyzed as continuous variables after log10 transformation. Associations with overall survival (OS) and progression-free survival (PFS) were assessed using multivariable Cox models adjusted for IMDC risk, age, and sex. A composite KIM-1–MAdCAM-1 risk score was developed to assess the incremental prognostic value of integrating these biomarkers. **Results:** Both KIM-1 and MAdCAM-1 levels were independently associated with OS and PFS in univariable analyses. In multivariable models including both biomarkers and adjusted for age, sex, and IMDC risk, higher KIM-1 levels remained associated with worse survival (OS: HR 1.57, 95% CI 1.28–1.93), whereas higher MAdCAM-1 levels were associated with improved survival (OS: HR 0.37, 95% CI 0.15–0.92). No significant interaction was observed between KIM-1 and MAdCAM-1, nor between either biomarker and treatment arm for OS or PFS. A composite KIM-1–MAdCAM-1 risk score was strongly associated with clinical outcomes. Patients in the highest-risk quartile had significantly worse PFS (median: 8.3 [5.7–11.1] vs 19.4 [13.8–NR] months) and OS rate (at 18 months: 65.0% [57.3–73.8] vs 90.0% [85.0–95.2]) compared to the lowest-risk quartile, across both treatment arms (Table). A joint KIM-1–MAdCAM-1 model demonstrated improved discrimination compared with either biomarker alone ($p < 0.001$), and the addition of both biomarkers to IMDC significantly improved OS discrimination (C-index 0.73 vs 0.67; $p < 0.001$). **Conclusions:** KIM-1 and MAdCAM-1 provide complementary and non-redundant prognostic information in mRCC. Their integration into a composite risk score significantly improves risk stratification beyond either biomarker alone and beyond IMDC criteria. These findings support a multi-axis circulating biomarker approach to prognostication in mRCC. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; CA258442; Dana-Farber/Harvard Cancer Center Kidney; CA101942-16; Dana-Farber/Harvard Cancer Center; CA006516-56.

Association of KIM-1–MAdCAM-1 composite score quartiles with progression-free and overall survival in the overall study cohort and by treatment arm.

KIM-1–MAdCAM-1 Composite Score	Entire Cohort HR (95% CI)	Avelumab + Axitinib HR (95% CI)	Sunitinib HR (95% CI)
Progression-Free Survival (Q4 vs Q1)	2.12 (1.56–2.87)	2.00 (1.31–3.05)	2.20 (1.41–3.43)
Overall Survival (Q4 vs Q1)	4.67 (2.71–8.05)	3.61 (1.75–7.44)	5.89 (2.54–13.7)

HR, hazard ratio; CI, confidence interval; Q, quartile.

Final analysis of the TiNivo-2 phase 3 trial: Long-term outcome of tivozanib (Tivo) in patients with metastatic renal cell carcinoma (mRCC).

Robert J. Motzer, Bradley Alexander McGregor, Laurence Albiges, Javier Molina Cerrillo, Philippe Barthelemy, Maria T. Bournon, Benjamin Garmez, Sheik Emambux, Arnab Basu, Raffaele Ratta, Pedro C. Barata, Jeffrey Thomas Yorio, Helen Moon, Alex Chehraz-Raffle, Roberto Iacovelli, Ralph J. Hauke, Rana R. McKay, Kathryn E. Beckermann, Moshe C. Ornstein, Toni K. Choueiri; Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Department of Medical Oncology, Gustave Roussy, Paris Saclay University, Villejuif, France; Ramon y Cajal University Hospital, Medical Oncology Department, Madrid, Spain; Department of Medical Oncology, Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France; Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN; Centre Hospitalier Universitaire de Poitiers, Poitiers, France; Division of Hematology and Oncology, Mayo Clinic Florida, Jacksonville, FL; Hopital Foch, Suresnes, France; Department of Medicine, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Texas Oncology, Austin, TX; SCPMG, Kaiser Permanente, Riverside, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; Università Cattolica del Sacro Cuore, Facoltà di Medicina e Chirurgia, Rome, Italy; Medical Oncology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Nebraska Cancer Specialists, Omaha, NE; Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA; Tennessee Oncology, Franklin, TN; Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: TiNivo-2 results showed that immune checkpoint inhibitor (ICI) rechallenge did not offer benefit to patients with mRCC, regardless of treatment sequencing (*Lancet*, 2024; 404: 1309). However, the data highlights activity for Tivo monotherapy in the post-ICI setting. Long term outcomes of the TiNivo-2 study are reported here. **Methods:** TiNivo-2 trial design and primary-endpoint results were previously reported: patients with mRCC were randomized to treatment with Tivo 0.89 mg once daily for 21/28 days plus Nivolumab (Nivo) at 480 mg every four weeks (Tivo/Nivo) or Tivo 1.34 mg once daily for 21/28 days. Here, long term progression free survival (PFS), overall survival (OS), and the safety profile are reported at final analysis. **Results:** At the data cutoff of 17 October 2025, 172 patients were randomized to Tivo (171 treated) and 171 patients were randomized to Tivo/Nivo (168 treated); median (m) follow up was 28.4 mo (95% CI 27.0–29.8) in Tivo versus 27.2 months (mo) (95% CI 26.1–28.5) in Tivo/Nivo. Survival outcomes and hazard ratios (HR) for the ITT population, 2L, and 3L populations are summarized in Table 1. In 2L, mPFS favored Tivo over Tivo/Nivo (9.23 mo [7.29, 11.04] vs 5.95 mo [5.42, 7.95]). Across subgroups, there were no differences in mOS. No new safety signals were observed with prolonged administration; the most common ≥ Grade 3 TEAE was hypertension occurring in 39 (22.8%) and 38 (22.6%) and of patients in the Tivo and Tivo/Nivo groups respectively. Other ≥ Grade 3 TEAEs included diarrhea (2.3% and 3.6%) and palmar-plantar erythrodysesthesia (0.6% and 1.2%) in the Tivo and Tivo/Nivo groups respectively. Treatment Related SAEs occurred in 15 (8.8%) and 18 (10.7%) of patients in Tivo and Tivo/Nivo groups respectively. **Conclusions:** This final analysis of patients in the TiNivo-2 study highlights the sustained efficacy Tivo in mRCC with a consistent safety profile. Together, these findings support durable clinical benefit and tolerability of Tivo in the post-ICI treatment setting in RCC, an area of high unmet need (NCT04987203). Clinical trial information: NCT04987203. Research Sponsor: AVEO Pharmaceuticals, Inc.

Parameter	By ITT		2L setting		3L setting	
	Tivo (0.89mg) /Nivo (n=171)	Tivo (1.34mg) (n=172)	Tivo (0.89mg) /Nivo (n=111)	Tivo (1.34mg)(n=105)	Tivo (0.89mg) /Nivo (n=60)	Tivo (1.34mg)(n=67)
mPFS, months (95% CI)	5.72 (4.37-7.43)	7.43 (5.52-9.23)	5.95 (5.42, 7.95)	9.23 (7.29, 11.04)	5.45 (3.15, 9.56)	5.44 (2.10, 7.36)
mPFS HR	0.96 (0.76, 1.21)		1.08 (0.80, 1.46)		0.77 (0.52, 1.15)	
mOS, months (95% CI)	23.85 (19.71-NR)	22.93 (18.14- NR)	29.50(21.06, NR)	23.52 (18.33, NR)	19.71 (10.81, 31.90)	22.70 (11.79, NR)
mOS HR	0.95 (0.70, 1.28)		0.78 (0.53, 1.16)		1.13 (0.70, 1.81)	

NR, not reached.

Explainable AI to predict molecular classes of renal cell carcinoma from digital pathology images.

Jordan Krull, Mirage Modi, Mingjia Li, Amir Mortazavi, Eric A. Singer, W. Kimryn Rathmell, Qin Ma, Yuanquan Aaron Yang; Department of Biomedical Informatics, College of Medicine, The Ohio State University, Columbus, OH; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Urologic Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: There is an unmet need to develop rapidly deployable and reliable biomarkers to guide treatment decisions in clear cell renal cell carcinoma (ccRCC). Transcriptome-based molecular classification is promising in predicting differential clinical outcomes to angiogenesis blockade alone or with an immune checkpoint inhibitor (ICI), but these approaches require molecular profiling that is costly and time-consuming. This study evaluates whether explainable artificial intelligence (AI) can accurately predict molecular classes of ccRCC from diagnostic H&E slides. This approach enables scalable, pathology-based assessment of treatment response-related biology without the need for additional tissue or sequencing. **Methods:** We acquired digital whole slide images of H&E stained primary ccRCC tumors from TCGA, OSU Total Cancer Care Alliance, and an in-house built set of selected biopsies. RNA-Seq cluster assignments from IMmotion151 study were reconstructed from published gene log-fold-change cluster enrichment scores and non-negative least squares regression on matching RNA-Seq of our samples. After assigning samples to their highest scoring group, we trained a multi-group attention-based multiple-instance learning (ABMIL) classifier to predict RNA-Seq groups from digital whole slide images broken into 112um patches and encoded using UNI foundation model embeddings. **Results:** A total of 555 cases with both H&E and RNA-seq data were included. Class prediction from RNA-Seq were 40% Angio-Stromal, 30% Complement-Ox, 16% Angio, 8% Teff-Prolif, 4% Prolif, 2% Stromal-Prolif and 0% snoRNA. Predicting these classes from H&E-stained images, showed AUROC values of 0.76 (Angio-Stromal), 0.78 (Complement-Ox), 0.83 (Angio), 0.85 (Teff-Prolif), 1.00 (Prolif) and 0.91 (Stromal-Prolif) respectively. Similar AUROC values with more modest curves were seen on a hold-out set (10%) where Angio-Stromal/Complement-Ox (0.61/0.61) and Teff-Prolif (0.59) were the lowest AUROC values and Prolif (0.99) was the highest. Importantly, incorrect predictions most often yielded a group prediction where the predicted group shared some biological identity with the ground truth group label (eg. Angio-Stromal and Angio). We also utilized the attention values from ABMIL to evaluate spatial prediction saliency, which showed the model focused primarily on tumor regions, even for predictions of primarily stromal defined classes. **Conclusions:** Our results demonstrate that diagnostic H&E slides contain histologic features that can predict ccRCC molecular subsets using explainable AI. Supporting scalable pathology-based inference of tumor biology linked to treatment response. Research Sponsor: None.

Spatial multiomic profiling to identify de-differentiated tumor phenotypes and exhausted T cell niches in rhabdoid and sarcomatoid RCC.

Zachary Alan Yochum, Sayed Matar, Peter Humphrey, Adebowale Adeniran, David A. Braun; Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; Yale School of Medicine, New Haven, CT; Department of Pathology, Yale School of Medicine, New Haven, CT

Background: Rhabdoid and sarcomatoid (S/R) differentiation are high-grade dedifferentiated states that can arise across renal cell carcinoma (RCC) subtypes. Although associated with poor patient prognosis, S/R RCC paradoxically exhibits increased sensitivity to immune checkpoint blockade. The mechanisms underlying this aggressive, yet immunotherapy-responsive phenotype remain unclear. Spatial multi-omic profiling offers a powerful framework to interrogate tumor-intrinsic and microenvironmental programs that account for this phenotype. Here, we applied spatial multi-omic analyses to treatment-naïve clear cell RCC specimens from seven patients, enabling direct comparison of sarcomatoid, rhabdoid, and clear cell regions captured within the same tissue sections. **Methods:** Hematoxylin and eosin (H&E)–stained sections from seven FFPE patient samples were reviewed and annotated by a genitourinary pathologist to identify discrete regions of sarcomatoid, rhabdoid, or clear cell morphology. Annotated FFPE samples were processed by Singular Genomics using the G4X spatial multi-omic platform, which enables quantification of 315 RNA transcripts, 14 protein targets, and fluorescent H&E imaging. **Results:** Initial spatial multi-omic profiling resolved distinct tumor regions with clear cell biology alongside areas exhibiting rhabdoid or sarcomatoid features. Comparative analysis of immune infiltrates across these regions revealed enrichment of both T cells and B cells within rhabdoid regions. In addition, T cells localized to rhabdoid and sarcomatoid regions displayed distinct phenotypic states compared with those in clear cell regions. Differential gene expression (DGE) analysis of T cells from rhabdoid and sarcomatoid regions relative to clear cell RCC demonstrated upregulation of activation markers (*CD69*, *IL2RA*), exhaustion markers (*LAG3*, *PDCD1*), and cytotoxic genes (*GZMA*, *GZMK*, *NKG7*). Parallel analysis of tumor cell transcriptional programs further highlighted distinct tumor biology across histologic regions. Sarcomatoid tumor cells exhibited increased expression of genes associated with cellular stress, inflammation, and epithelial–mesenchymal transition (EMT), including *IGFBP7* and *FOS*. In contrast, rhabdoid tumor cells showed upregulation of antigen–presentation machinery (*HLA-A*, *TAP1/2*) along with elevated expression of EMT-associated genes (*MET*, *VCAM1*, and *CD44*). **Conclusions:** Spatial multi-omic analysis of S/R RCC revealed distinct immune and transcriptional programs across sarcomatoid, rhabdoid and clear cell regions. T cells within S/R regions exhibited activated and exhausted phenotypes, while tumor cell characterization of S/R cells reveals upregulation of stress, inflammatory and antigen–presentation machinery, features that may underlie the sensitivity of S/R RCC to immune checkpoint inhibitors. Research Sponsor: None.

Association of baseline quality of life (QOL) and early death in patients with metastatic renal cell carcinoma (mRCC) in the real-world prospective observational ODYSSEY study.

Michael R. Harrison, Elizabeth Wulff, Yasser Ged, Benjamin L. Maughan, Nrupen Anjan Bhavsar, Leonard Joseph Appleman, Yousef Zakharia, Brian Addis Costello, Deepak Kilari, Sorab Gupta, Melyssa Bratton, Paul Monk III, Ulka N. Vaishampayan, Tracy L. Rose, Sarah Jabusch, Kimberly T. Ward, Yuan Wu, Courtney Page, Tian Zhang, Daniel J. George, ODYSSEY Study Group; Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC; University of Kansas Medical Center, Kansas City, KS; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT; Department of Surgery, Duke University Health System, Durham, NC; University of Pittsburgh, Pittsburgh, PA; University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA; Division of Medical Oncology, Mayo Clinic Rochester, Rochester, MN; Cancer Center-Froedtert Hospital & Medical College of Wisconsin, Milwaukee, WI; Geisinger Health System, Wilkes-Barre, PA; Ochsner Health, New Orleans, LA; The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; Division of Oncology, The University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Duke Clinical Research Institute, Durham, NC; Department of Biostatistics and Bioinformatics, Duke Cancer Institute, Durham, NC; Department of Internal Medicine, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Duke Cancer Institute Center for Prostate & Urologic Cancers, Durham, NC

Background: Baseline QOL has been linked to survival in mRCC therapy clinical trials (Cella, 2024); however, there is a paucity of prospectively collected real-world QOL data across front-line management strategies. We used data from ODYSSEY to examine the relationship between baseline QOL and early death. **Methods:** ODYSSEY is a multi-site, prospective observational study of 468 US pts with mRCC. Pts must have mRCC (any histology); have no prior systemic therapy (ST) or be within 3 months of starting 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. Early death was defined as death within 12 months post-enrollment. All pts with non-missing FKSI-19 or FKSI-DRS at enrollment were included. Cumulative event probabilities as a function of time were stratified by either $<$ or $\geq$ median QoL value and plotted as a step function vs time since enrollment to create cumulative event curves. To determine association between QoL at enrollment and early death, separate Cox proportional hazards models (unadjusted and adjusted) for time-to-first-event as a function of baseline QoL were fit. The adjusted model controlled for the following baseline covariates: IMDC risk (favorable vs intermediate or poor), histology (clear cell vs non). **Results:** As of 1/5/26, 468 pts were enrolled; 425 had non-missing FKSI-19 or FKSI-DRS at enrollment (329 immediate ST, 96 deferred ST [DST]). ST included 129 IO-IO, 108 IO-TKI, 92 Other. DST included 57 Active Surveillance, 22 Local Therapy Planned, 17 Other/Missing. 209 and 190 pts have $<$ median FKSI-19 (score = 59) and FKSI-DRS (score = 29), respectively; 216 and 235 pts have $\geq$ median FKSI-19 and FKSI-DRS, respectively. Those below the median have lower rates of nephrectomy, worse IMDC risk and KPS, shorter time since RCC diagnosis, and higher rates of bone metastasis (all $p < 0.05$). Cumulative event probabilities for death at 12 months are 21% and 7% in those $<$ and $\geq$ median baseline FKSI-19, respectively; and 21% and 7% in those $<$ and $\geq$ median baseline FKSI-DRS, respectively. For FKSI-19, the unadjusted hazard ratio (HR) for early death is 0.55 (95% CI: 0.43 – 0.70; $p < 0.001$) and adjusted HR is 0.65 (0.49 – 0.85; $p = 0.002$) per 1 SD higher score. For FKSI-DRS, the unadjusted HR for early death is 0.57 (95% CI: 0.46 – 0.71; $p < 0.001$) and adjusted HR is 0.66 (0.51 – 0.86; $p = 0.002$) per 1 SD higher score (higher score indicates better QOL). **Conclusions:** Across management strategies in our ODYSSEY cohort of systemic therapy naïve mRCC patients, better baseline QOL was associated with better survival. This is to our knowledge the largest reported real world mRCC cohort with prospectively collected PROs. Future analyses will focus on association of outcomes with longitudinal PROs. Clinical trial information: NCT04919122. Research Sponsor: Bristol Myers Squibb; Exelixis; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.; Pfizer.

Clinical and genomic predictors of outcomes in patients (pts) with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin and pembrolizumab (EVP): UNITE study analysis.

Elise Y. Cai, Li Zhang, Kevin R. Reyes, Zachariah Thomas, Cindy Y. Jiang, Eugene Oh, Tanya Jindal, Jeffrey Yinhong Zhong, Salvador Jamie Casas, Catherine Fahey, Shilpa Gupta, Sumit Shah, Arnab Basu, Petros Grivas, Abhishek Tripathi, Jason Robert Brown, Omar Alhalabi, Irene Tsung, Matthew T. Campbell, Vadim S. Koshkin, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; University of California, San Francisco, San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Michigan Medical School, Ann Arbor, MI; School of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH; Case Western Reserve University School of Medicine, Cleveland, OH; City of Hope Comprehensive Cancer Center, Duarte, CA; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH; Stanford Cancer Center, Stanford, CA; University of Alabama at Birmingham, Birmingham, AL; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Rogel Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI

Background: EVP is the recommended 1st line (1L) therapy for pts with aUC and is moving into the perioperative setting. There is limited understanding of clinical factors and biomarkers predictive of EVP outcomes. **Methods:** We analyzed pts with aUC treated with EVP in the multi-site retrospective UNITE study. χ^2 test and logistic regression were used to assess observed response rate (ORR) and disease control rate (DCR). Log-rank test and Cox proportional hazard models were used to assess progression-free survival (PFS) and overall survival (OS) from EVP start. Multivariable analysis (MVA) included age, sex, race, ECOG performance status (PS), neutrophil-to-lymphocyte ratio (NLR), albumin, hemoglobin (Hgb), primary tumor site, histology, treatment line, and metastatic sites as covariates. **Results:** A total of 521 pts with aUC from 16 sites received EVP. Median age was 71, 75% were male, 81% were Caucasian, 76% had ECOG PS 0-1, and 72% were treated with 1L EVP. 74% had lower tract primary tumor, 65% pure urothelial histology, 18% liver metastases (mets), 43% non-liver visceral mets, and 28% lymph node (LN)-only mets. At 8.1 mos median follow-up from EVP start, the overall cohort had ORR 55%, DCR 82% [16% complete response (CR), 39% partial response (PR), 27% stable disease (SD)], median PFS (mPFS) 6.5 mos, and median OS (mOS) 19.8 mos. For 1L EVP pts, at 9.8 mos median follow-up, ORR was 59%, DCR 83% (20% CR, 39% PR, 24% SD), mPFS 10.1 mos, and mOS 23.3 mos. In both the overall cohort and 1L EVP pts, clinical factors associated with longer PFS and OS included ECOG PS 0-1, Caucasian race, albumin ≥ 3.5 g/dL, Hgb ≥ 10 g/dL, NLR < 5 , and absence of visceral mets. CR was associated with ECOG PS 0-1 (OR 3.6, 95% CI 1.4-12.5, $p = 0.02$), Hgb ≥ 10 g/dL (OR 2.3, 95% CI 1.2-4.8, $p = 0.02$), NLR < 5 (OR 2.7, 95% CI 1.5-5.3, $p = 0.002$), LN-only mets (HR 3.8, 95% CI 1.7-9.8, $p = 0.003$), immunotherapy-naïve status (OR 4.1, 95% CI 1.4-17, $p = 0.02$), and 1L EVP for aUC (OR 3.3, 95% CI 1.7-7.3, $p = 0.001$). Pts with CR had longer mPFS than pts with PR or SD (26.5 vs. 14.5 vs. 7.5 mos, $p < 0.001$) and longer mOS (NR vs. 33.4 vs. 14.5 mos, $p < 0.001$). Among 315 pts with molecular profiling, the most common alterations were in *TERTp* (55%), *TP53* (45%), *FGFR3* (22%), *ARID1A* (19%), *KMT2D* (18%), *PIK3CA* (18%), and *CDKN2A/B* (17%). In MVA, *KMT2D* alterations were associated with lower CR rate (6% vs. 19%, $p = 0.05$), shorter mPFS (5.0 vs. 8.0 mos, $p = 0.04$), and shorter mOS (12.0 vs. 20.0 mos, $p = 0.04$). Very high tumor mutational burden (≥ 15 mut/Mb) was associated with higher DCR (97% vs. 79%, $p = 0.04$) but no significant difference in PFS or OS. **Conclusions:** In this large real-world cohort, ECOG PS, metastatic site, treatment line, and prior immunotherapy exposure were associated with EVP outcomes. *KMT2D*-altered aUC may represent a high-risk molecular subset with worse outcomes. Further validation in prospective cohorts is needed. Research Sponsor: None.

Real-world overall survival outcomes of belzutifan treatment in advanced renal cell carcinoma.

Elshad Hasanov, Zuhair Majeed, Antonio Faieta, Betul Gok Yavuz, Edmund Folefac, Paul Monk III, Ahmad Shabsigh, Steven K. Clinton, Amir Mortazavi, Eric A. Singer, Merve Hasanov; Pelotonia Institute for Immuno-Oncology and Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University, Columbus, OH; The University of Chicago, Chicago, IL; The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Belzutifan, a hypoxia-inducible factor-2 α inhibitor, is an emerging therapy for advanced renal cell carcinoma (RCC) that demonstrated significant benefit over everolimus in the LITESPARK-005 trial. We aimed to validate these findings in a real-world setting and identify clinical prognostic factors within a large, multi-institutional cohort. **Methods:** We conducted a retrospective cohort study, using Epic Cosmos, of adults with RCC who initiated Belzutifan on or after the FDA Approval date (December 14, 2023) to Dec 20, 2025, ensuring at least one month of follow-up prior to the query date. Overall survival (OS) was measured from the treatment start date to death, with censoring at the last clinical encounter. Survival was estimated using Kaplan–Meier methods. Associations between baseline clinical and laboratory variables and OS were evaluated using univariable Cox proportional hazards models with false discovery rate (FDR) correction. **Results:** A total of 2,844 patients were included; the median age was 66 years, 72% were male, and 51.2% had documented tobacco use. The OS probabilities were 80.9%, 68.1%, 58.3%, and 53.2% at 6, 12, 18, and 24 months, respectively, and comparable to the LITESPARK-005 trial. Among clinical variables, tobacco use was associated with worse survival (HR 1.24 [95% CI 1.08–1.44], FDR = 0.014), whereas female sex (HR 0.78 [0.66–0.92], FDR = 0.014) and higher BMI (HR 0.96 [0.95–0.98], FDR <0.001) were associated with improved outcomes. Markers of nutritional and hematologic reserve were strongly protective, including higher Albumin (HR 0.46 [0.41–0.52], FDR <0.001), Total Protein (HR 0.77 [0.70–0.89], FDR <0.001), Hemoglobin (HR 0.90 [0.87–0.93], FDR <0.001), RBC (HR 0.69 [0.62–0.75], FDR <0.001), and MPV (HR 0.90 [0.84–0.96], FDR = 0.002). Inflammatory and immune markers demonstrated divergent effects: higher Lymphocytes (HR 0.53 [0.46–0.61], FDR <0.001) and Lymphocyte-to-Monocyte Ratio (HR 0.75 [0.71–0.80], FDR <0.001) predicted favorable outcomes. Conversely, worse survival was associated with elevated RDW (HR 1.14 [1.11–1.17], FDR <0.001), Monocytes (HR 1.71 [1.34–2.20], FDR <0.001), Basophil-to-Lymphocyte Ratio (HR 2.39 [1.20–4.77], FDR = 0.019) and Neutrophils (HR 1.06 [1.04–1.07], FDR <0.001). Higher Corrected Calcium (HR 1.43 [1.30–1.57], FDR <0.001) and Total Bilirubin (HR 1.13 [1.04–1.22], FDR = 0.005) were associated with inferior outcomes. **Conclusions:** In the largest real-world cohort to date, overall survival after belzutifan initiation mirrored LITESPARK-005, supporting its effectiveness in routine practice. Baseline nutritional, hematologic, and immune markers were associated with improved survival, while systemic inflammation and metabolic dysfunction predicted worse outcomes, highlighting the prognostic value of routine clinical variables. Research Sponsor: Pelotonia Institute for Immuno-Oncology (PIIO) Recruitment Startup Fund; The Ohio State University Comprehensive Cancer Center (OSUCCC).

Real-world clinical outcomes by HER2 expression in locally advanced/metastatic urothelial carcinoma (la/mUC): Results from the global SGNDV-003 retrospective study.

Vadim S. Koshkin, Christine Abraham Jaillon, Nataliya Mar, Denis Maillet, Shahrokh F. Shariat, Parminder Singh, Ali Raza Khaki, Alexandra Drakaki, Laura Graham, Axel Stuart Merseburger, Jiaoti Huang, Matthew D. Galsky, Lei Yin, Kevin M. Sokolowski, Dingfeng Jiang, Shaparak Lonning, Wei Zhang, Hong Yu, Earle F. Burgess; University of California, San Francisco, CA; Hospital Foch, Suresnes, France; University of California Irvine, Irvine, CA; Centre Hospitalier Universitaire Lyon, Lyon, France; Medical University Vienna, Vienna, Austria; Mayo Clinic Arizona, Phoenix, AZ; Stanford Cancer Institute, Stanford, CA; University of California Los Angeles Medical Center, Los Angeles, CA; University of Colorado, Aurora, CO; University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; Duke University, Durham, NC; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Pfizer Inc., New York, NY; Pfizer Inc., Bothell, WA; Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Charlotte, NC

Background: Approximately 50–80% of patients (pts) with la/mUC have tumors with HER2 protein expression. As HER2-directed therapies enter development, a robust understanding of HER2 prevalence and real-world outcomes with standard-of-care (SOC) therapies across HER2 expression subgroups is needed. SGNDV-003 (NCT05902494) is a global retrospective chart review study in which HER2 status was assessed via central lab testing and outcomes were analyzed by HER2 status in pts with la/mUC. **Methods:** SGNDV-003, conducted 6/2023–7/2025, included pts with la/mUC who received ≥ 1 prior treatment (tx) (incl. 1 line of platinum-based chemotherapy [chemo]). HER2 status was centrally tested using a UC-specific investigational immunohistochemistry [IHC] and in situ hybridization (ISH) assays. HER2 status was defined as: HER2-positive (IHC3+ or IHC2+/ISH+), HER2-low (IHC2+/ISH- or IHC1+), HER2-expressing (IHC3+, 2+, 1+), and HER2-zero (IHC0). Index line of therapy (LOT) was defined as the first LOT received after platinum-based chemo. Outcomes included real-world objective response rate (rwORR) (per RECIST 1.1 or physician-assessed response) to index LOT, real-world progression-free survival (rwPFS), and overall survival (OS) from start of index LOT. Data was analyzed via descriptive statistics. **Results:** A total of 353 pts with la/mUC and available HER2 status were analyzed (male, 76%; median age, 70 years). 70% of pts were HER2-expressing (19% HER2-positive, 51% HER2-low); 30% were HER2-zero. Disease characteristics were well balanced by HER2 status. Index LOT tx and real-world outcomes are shown in the Table. Immuno-oncology therapies (IO) and enfortumab vedotin (EV) were the most common index LOTs. For IO, rwORRs were 21% for HER2-expressing and 17% for HER2-zero. For EV mono, rwORRs were 36% (HER2-expressing) and 38% (HER2-zero), respectively. **Conclusions:** This global study provides a robust estimate of HER2 distribution in la/mUC based on standardized central lab testing, showing high prevalence of HER2 expression. Real-world outcomes with current SOC therapies were broadly consistent across HER2 subgroups, establishing an important benchmark for the clinical development of HER2-directed therapies in this setting. Research Sponsor: Seagen Inc. Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	HER2-positive (n=67)	HER2-low (n=181)	HER2-expressing (n=248)	HER2-zero (n=105)	Total (n=353)
Real-world Outcomes					
rwORR, n (%)	17 (25.4)	50 (27.6)	67 (27.0)	22 (21.0)	89 (25.2)
[95% CI]	[15.5, 37.5]	[21.3, 34.7]	[21.6, 33.0]	[13.6, 30.0]	[20.8, 30.1]
Median rwPFS (95% CI), mo	2.8 (2.0, 4.1)	3.7 (2.7, 5.1)	3.0 (2.7, 4.5)	2.6 (2.1, 3.4)	2.9 (2.6, 3.5)
Median OS (95% CI), mo	12.2 (9.3, 16.5)	11.5 (9.5, 13.5)	11.9 (10.3, 13.4)	7.7 (5.9, 9.9)	10.8 (9.1, 12.3)
Index LOT, n%					
IO	37 (55)	94 (52)	131 (53)	65 (62)	196 (56)
EV mono	17 (25)	51 (28)	68 (27)	21 (20)	89 (25)
Chemo	10 (15)	24 (13)	34 (14)	12 (11)	46 (13)
Other tx	3 (5)	14 (8)	17 (7)	7 (7)	24 (7)

Zelenectide pevedotin (BT8009) monotherapy in previously treated metastatic urothelial carcinoma (mUC): Update on Duravelo-1.

Oscar Reig Torras, Laurence Crouzet, Andrea Necchi, Capucine Baldini, M. Julia Lostes-Bardaji, Louise Carter, Bernard Gaston Doger de Spéville, Antoine Italiano, Loïc Verlingue, Valentina Boni, Ignacio Duran, Benjamin Garmez, Matthew D. Galsky, Gerald Steven Falchook, Leslie DeMars, Gladys Brown, Cong Xu, Elisa Fontana; Hospital Clínic de Barcelona, Barcelona, Spain; Unicancer, Centre Eugène Marquis, Rennes, France; Vita-Salute San Raffaele University and IRCCS Ospedale San Raffaele, Milan, Italy; Gustave Roussy Cancer Campus, Villejuif, France; Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; The University of Manchester and The Christie NHS Foundation Trust, Manchester, United Kingdom; Start-Madrid Phase 1 Clinical Unit, START Madrid-FJD-Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Early Phase Trials Unit, Institut Bergonié, and University of Bordeaux, Bordeaux, France; Phase 1 Clinical Unit, Centre Léon Bérard, Lyon, France; NEXT Madrid, University Hospital Quirónsalud Madrid, Madrid, Spain; Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; Sarah Cannon Research Institute, Nashville, TN; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Sarah Cannon Research Institute at HealthONE, Denver, CO; Clinical Development, Bicycle Therapeutics, Cambridge, MA; Biostatistics, Bicycle Therapeutics, Cambridge, MA; Drug Development, Sarah Cannon Research Institute UK, London, United Kingdom

Background: Zelenectide pevedotin (zele, formerly BT8009) is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4, a protein that is overexpressed in mUC and other cancers. Zele has a lower molecular weight (4.2 kDa) and a shorter plasma half-life (<1 hour) than antibody drug conjugates (ADCs), with potential to rapidly penetrate solid tumors and minimize healthy tissue exposure. Here, we present updated safety and efficacy results of zele monotherapy in enfortumab vedotin (EV)-naïve patients with mUC from the Phase 1/2 Duravelo-1 study (NCT04561362). **Methods:** Eligible patients had previously treated unresectable mUC, creatinine clearance ≥ 50 mL/min, prior anti-PD-1/PD-L1 exposure, had progressed on or were ineligible for platinum-based chemotherapy, and had not received EV. All patients treated with the recommended Phase 2 dose of zele monotherapy 5 mg/m² once weekly across the dose-escalation and dose expansion phases were included in the analysis. **Results:** As of July 1, 2025, 53 patients with a median age of 63 years (range 25–84) and a median of 2 (range 1–7) prior lines of therapy were included. Median time on treatment was 4.4 months and maximum duration was 24.9 months, and median follow-up time was 9.9 months (range 0.5–43.9). Median progression-free survival was 5.4 months (95% CI 2.3–7.1). Confirmed objective response rate (cORR) in all patients was 32% (n=17/53), and disease control rate (DCR) was 66% (n=35/53), including 2 complete responses and 15 partial responses (PR); 3 additional patients had unconfirmed PR. Of the 13 patients who had received prior taxane therapy, cORR was 31% and DCR was 69%, including 4 PR and 5 with stable disease. Median duration of response was 10.0 months (95% CI 5.3–16.6) among patients with confirmed responses (n=17). Nausea (36%), asthenia (28%), and diarrhea (28%) were the most common treatment-related adverse events (TRAEs). TRAEs of Grade ≥ 3 occurred in 25% of patients and serious TRAEs occurred in 9%. TRAEs led to treatment withdrawal in 4% of patients. Grade 3 TRAEs of clinical interest (AECIs) were single reports of skin reaction and hyperglycemia (n=1 each, 2%). Grade 1–2 treatment-related AECIs of peripheral neuropathy were reported in 47% of patients and were all sensory-based, with 1 patient requiring treatment withdrawal. Grade 1–2 treatment-related skin reaction and eye disorder AECIs were reported in 15% and 13%, respectively. **Conclusions:** Zele monotherapy at 5 mg/m² once weekly continues to demonstrate an encouraging efficacy profile and a promising safety profile with the potential to differentiate from ADCs in EV-naïve patients with mUC. Antitumor activity was preserved in patients with exposure to taxanes. Treatment withdrawal resulting from zele-related AECIs was uncommon. A Phase 2/3 study of zele in patients with locally advanced or mUC (NCT06225596; Duravelo-2) is currently active. Clinical trial information: NCT04561362. Research Sponsor: BicycleTx Ltd.

Zelenectide pevedotin (BT8009) plus pembrolizumab in 1L cisplatin-ineligible locally advanced/metastatic urothelial carcinoma: Update on Duravelo-1 B7.

Ignacio Duran, Patrizia Giannatempo, Matthew D. Galsky, Valentina Boni, Andrea Necchi, Antoine Italiano, Meredith McKean, Loic Verlingue, Leslie DeMars, Gladys Brown, Cong Xu, Oscar Reig Torras; Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; NEXT Madrid, University Hospital Quirónsalud Madrid, Madrid, Spain; Vita-Salute San Raffaele University and IRCCS Ospedale San Raffaele, Milan, Italy; Early Phase Trials Unit, Institut Bergonié, and University of Bordeaux, Bordeaux, France; Sarah Cannon Research Institute, Nashville, TN; Phase 1 Clinical Unit, Centre Léon Bérard, Lyon, France; Clinical Development, Bicycle Therapeutics, Cambridge, MA; Biostatistics, Bicycle Therapeutics, Cambridge, MA; Hospital Clínic de Barcelona, Barcelona, Spain

Background: Zelenectide pevedotin (zele, formerly BT8009) is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4 and conjugated to MMAE. Zele has a lower molecular weight (4.2 kDa) and a shorter plasma half-life (< 1 hour) than antibody drug conjugates (ADCs), with potential to rapidly penetrate solid tumors and minimize healthy tissue exposure. Preliminary results of zele + pembrolizumab (pembro) in previously untreated, cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (la/mUC) patients (pts) (expansion cohort B7, NCT04561362; Duravelo-1), showed promising antitumor activity and a generally tolerable safety profile (Giannatempo et al., 2025). Here, we present updated results with extended follow-up and further efficacy data. **Methods:** Cisplatin-ineligible pts by Galsky criteria who had received no prior systemic anticancer treatment for la/mUC were eligible. Pts received IV zele 5 mg/m² on Days (D)1/8/15 + pembro 200 mg on D1 of a 21-D cycle. The primary endpoint was confirmed objective response rate (cORR) per Investigator using RECIST v1.1. Secondary endpoints included safety and additional efficacy endpoints. Treatment-related adverse events (TRAEs) were determined for all pts who received at least one dose of study drugs. **Results:** As of July 1, 2025, 22 pts were treated: median age 77 years, 45% had ECOG performance status (PS) of 2, and 45% had creatinine clearance < 60 mL/min. Median duration of treatment for zele and pembro was 23.4 weeks (range 1.0–84.1) and 26.9 weeks (range 3.0–85.9), respectively. Median follow-up was 11.8 months (range 1.0–19.4); 14 pts remained on study at the time of data analysis. Median progression-free survival (mPFS) was 13.0 months (95% CI 3.8–NE). cORR was 50% (n = 11/22), and disease control rate was 82% (n = 18/22), including 5 complete responses and 6 partial responses (PR); 2 additional pts had unconfirmed PRs. Median duration of response (mDOR) was not mature. The most common Gr ≥3 TRAEs included ALT increase (18%) and neutropenia and asthenia (14% each). Of AEs of clinical interest (AECIs), treatment-related Gr 3 events included peripheral neuropathy (14%; leading to drug withdrawal in 2 pts) and skin reactions (9%; these events were not serious and did not lead to withdrawal); no Gr 4 or 5 treatment-related AECIs occurred. **Conclusions:** Treatment with zele + pembro has promising clinical benefits in pts with la/mUC and a historically poor prognosis with first-line therapies (~50% ECOG PS of 2), including: mPFS of 13.0 months, 50% cORR, and mDOR not reached. Additionally, zele + pembro demonstrates a safety profile with the potential to differentiate from ADC combinations, including no skin-related serious AEs. These data support the Phase 2/3 study of zele as monotherapy and in combination with pembro versus chemotherapy in pts with la/mUC (NCT06225596; Duravelo-2). Clinical trial information: NCT04561362. Research Sponsor: BicycleTx Ltd.

Effect of on-treatment dose adjustments on the efficacy of enfortumab vedotin and pembrolizumab (EVP) in advanced urothelial carcinoma (aUC): A UNITE analysis.

Jeffrey Yinong Zhong, Albert Jang, Tanya Jindal, Cindy Y. Jiang, Zachariah Thomas, Eugene Oh, Charles B. Nguyen, Dimitra Bakaloudi, Salvador Jaime-Casas, Abhishek Tripathi, Petros Grivas, Irene Tsung, Matthew T. Campbell, Omar Alhalabi, Melissa A. Reimers, Ali Raza Khaki, Zhengyi Chen, Pingfu Fu, Vadim S. Koshkin, Jason Robert Brown; Division of Solid Tumor Oncology, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; Division of Medical Oncology, Department of Oncology, Mayo Clinic Rochester, Rochester, MN; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Michigan Medical School, Ann Arbor, MI; City of Hope Comprehensive Cancer Center, Duarte, CA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; Division of Oncology, Department of Internal Medicine, Washington University in St. Louis, St. Louis, MO; Division of Oncology, Stanford University, Stanford, CA; Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH; Helen Diller Family Comprehensive Cancer Center, Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA

Background: EVP is the preferred 1st-line regimen for patients (pts) with aUC. EV-related toxicities are often managed with dose adjustments, such as reductions and holds. Analysis of EV monotherapy trials showed consistent survival outcomes despite dose adjustments. We hypothesized that on-treatment EV dose adjustments would not impact survival in these pts.

Methods: Pts with aUC treated with EVP in the multisite UNITE study were analyzed. Early dose reductions (DR) and holds were defined as occurring < 9 weeks from EVP start, with the remainder classified as late. Pts with DR at treatment start were excluded. Survival endpoints were progression-free survival (PFS) and overall survival (OS) from EVP start, assessed by Kaplan-Meier analysis and Cox models. Multivariable Cox analysis (MVA) included age (≥ 75 vs < 75), ECOG performance status (0-1 vs 2-3), Hgb level (< 10 vs ≥ 10) and liver metastases (present vs not). A time-dependent covariate was used to reduce immortal time bias. Complementary MVA landmark analyses were performed, aligned to the total number of treatment cycles received, with six analyses from cycles 2 to 7. **Results:** 360 pts from 17 sites were included (median age 70; 78% Caucasian; 76% male; 27% upper tract primary; 35% histology subtype component; 17% with liver metastasis; 78% frontline); median follow-up was 11.7 months (95% CI [10.79, 13.08]). Median number of cycles was 6 in pts with DR and 3 with no DR. Early DRs (100 pts [28%]) and holds (18 pts [5%]) were most commonly due to rash (28% of all early DRs and holds). Late DR (75 pts [21%]) and holds (50 pts [14%]) were most commonly due to neuropathy (52% of all late DRs and holds). Pts with early or late DR had longer PFS and OS vs those who did not (Table); however, there was no significant PFS or OS difference with dose hold vs no hold (PFS HR 0.65, 95%CI (0.40, 1.05), $p = 0.08$; OS HR 0.70, 95%CI (0.39, 1.27), $p = 0.24$). In landmark analyses, about 50% of pts had DR; no significant difference in PFS or OS was observed at most landmarks, except for longer OS in the DR cohort at cycle 4 (HR 0.53, 95% CI (0.29, 0.98), $p = 0.042$) and cycle 5 (HR 0.43, 95% CI (0.19, 0.99), $p = 0.048$). **Conclusions:** In this real-world retrospective analysis, EVP efficacy was maintained despite DR and dose holds. Survival difference noted in the time-dependent analyses were not consistently reproduced in landmark analyses, suggesting exposure-related selection bias rather than causal effect. Prospective studies are warranted to validate these hypothesis-generating findings. Research Sponsor: None.

Association of EV DR with PFS/OS (time-dependent analyses).

DR vs no DR outcomes	Early DR		Late DR	
	UVA HR (95% CI), p	MVA HR (95% CI), p	UVA HR (95% CI), p	MVA HR (95% CI), p
PFS	0.50 (0.35, 0.72), <.001	0.56 (0.38, 0.84), 0.005	0.32 (0.21, 0.49), <.001	0.36 (0.23, 0.57), <.001
OS	0.51 (0.32, 0.79), 0.003	0.57 (0.35, 0.92), 0.022	0.26 (0.15, 0.45), <.001	0.31 (0.17, 0.55), <.001

Interim analysis results from Duravelo-2: Zelenectide pevedotin (zele; BT8009) in patients (pts) with previously treated locally advanced/metastatic urothelial carcinoma (la/mUC).

Daniel P. Petrylak, Yohann Lorient, Cong Xu, Ananya De, Hongmei Xu, Michael Method, Leslie DeMars; Yale School of Medicine, New Haven, CT; University Paris-Saclay, Gustave Roussy, Villejuif, France; Bicycle Therapeutics, Cambridge, MA

Background: Zele is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4, a protein overexpressed in la/mUC. There remains an unmet need in la/mUC for safer and more tolerable treatments. Here, we report an interim analysis (IA) for zeles monotherapy dosage selection from the Phase 2/3 Duravelo-2 study (NCT06225596/BT8009-230) in previously treated pts with la/mUC. **Methods:** Adults with la/mUC were enrolled into 2 cohorts: previously untreated pts eligible for platinum-based chemotherapy (Cohort [Co]1) or pts with ≥ 1 prior systemic therapy (Co2). IA was conducted to determine the optimized dosage of zeles + pembrolizumab (Co1) or zeles monotherapy (Co2). Herein, we report IA results from Co2. Pts in Co2 were randomized 1:1 to zeles 5 mg/m² on Days [D]1/8/15 or zeles 6 mg/m² on D1/8 on a 21-D cycle. Dosage optimization included safety, efficacy, and pharmacokinetic data in pharmacometrics and utility score analyses to quantify benefit-risk. **Results:** IA was performed at 27 weeks of follow-up (N=30 each zeles dose group). Median zeles treatment (tx) duration was 4.80 months. Confirmed ORRs by BICR among randomized, dosed pts with measurable disease at baseline were 28% (8/29; 2 complete responses [CR], 6 partial responses [PR]; 95% CI 12.7–47.2) and 30% (8/27; 3 CR, 5 PR; 95% CI 13.8–50.2) with zeles 5 mg/m² and 6 mg/m², respectively. Zele-related adverse events (AEs) were reported in 93% (47% Gr ≥ 3) of pts at 5 mg/m² and 93% (52% Gr ≥ 3) at 6 mg/m². Gr ≥ 3 zele-related AEs for 6 mg/m² ($\geq 5\%$ pts) included neutrophil count decreased and neutropenia (10% each) and anemia, asthenia, and ALT increase (7% each). No zele-related Gr 5 AEs were reported at either dosage. Zele-related AEs of clinical interest (AECIs) for 6 mg/m² are summarized in the Table. Notably, no zele-related severe skin reactions of any Gr were reported at either dosage. Zele dose reductions and discontinuations due to zele-related AEs occurred in 24% and 0%, respectively, for 6 mg/m². At Week 27, a third of pts remained on tx. **Conclusions:** Zeles monotherapy at 5 mg/m² on D1/8/15 and 6 mg/m² on D1/8 on a 21-D cycle demonstrate encouraging response rates and safety profiles with the potential to differentiate from ADCs in previously treated pts. The 6 mg/m² D1/8 regimen provides a more favorable benefit-risk profile to meet the need for safer and more tolerable treatments, with enhanced potential for combinability and convenience, leading to fewer discontinuations. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

Zele-related AECIs in pts with previously treated la/mUC treated with zeles 6 mg/m² on D1/8 (N=30).

AECI, n (%)	Any Grade	Grade ≥ 3
Peripheral neuropathy	11 (38)	1 (3)
Skin reactions	8 (28)	0
Eye disorders	3 (10)	0
Hyperglycemia	1 (3)	1 (3)

Identifying optimized dosage for zelenectide pevedotin in locally advanced/metastatic urothelial carcinoma (la/mUC) using quantitative analyses.

Yasong Lu, Justin Bader, Cong Xu, Lei Xu, Leslie DeMars, Michael Method, Eric H. Westin, Hongmei Xu; Bicycle Therapeutics, Cambridge, MA

Background: Zelenectide pevedotin (zele; BT8009) is a Bicycle Drug Conjugate (BDC) comprising a highly selective bicyclic peptide targeting Nectin-4 linked to the cytotoxin monomethyl auristatin E (MMAE) via a cleavable linker. Zele demonstrated preliminary antitumor activity and a generally tolerable safety profile in patients (pts) with la/mUC in the Phase 1/2 Duravelo-1 trial (NCT04561362) [Reig, 2024; Giannatempo, 2025]. Zele is being evaluated in a randomized Phase 2/3 study at 2 dosages, 5 mg/m² on Days (D)1/8/15 and 6 mg/m² on D1/8 of a 21-D cycle, each as monotherapy or combined with pembrolizumab (P) in pts with la/mUC (NCT06225596, Duravelo-2) [Loriot, 2025]. After 30 pts in each dosage arm had 27 weeks follow-up (N=120 total), an interim analysis was conducted to select the optimized dosage for further development. **Methods:** Pharmacometric (PMx) and utility score analyses were conducted to quantify the benefit-risk comprehensively. For the PMx analysis, all pharmacokinetic (PK), overall response rate [ORR, assessed by investigator (INV) and/or blinded independent central reviewer (BICR)], and adverse event (AE) data [zele-related and treatment-emergent (TE) Gr ≥ 3 AE, Gr ≥ 3 neutropenia, Gr ≥ 2 gastrointestinal disorders, Gr ≥ 2 peripheral neuropathy, any Gr skin reactions, dose modifications] from Duravelo-1 and -2 were pooled and analyzed using population PK (PopPK) and exposure-response (ORR, AE) modeling. Simulations for ORR and AE probabilities were then generated for comparing dosages with balance of relevant pt characteristics. The utility score analysis was mainly based on Gr ≥ 3 zele-related TEAEs and ORR by BICR regardless of confirmation in Duravelo-2, with sensitivity analyses based on alternative safety and/or efficacy endpoints (TEAEs, confirmed ORR by BICR). **Results:** The datasets for PopPK, ORR, and AE analysis included 434, 203 (203 INV assessed, 114 BICR assessed), and 394 pts, respectively, mostly treated at the 5 or 6 mg/m² dosages. Modeling of ORR did not detect a significant difference between the dosages studied. ORR was impacted positively by P combination, negatively by baseline tumor size, but not by the assessor (INV vs BICR). The AE rates were significantly correlated with exposures of zele and/or MMAE. Between 5 mg/m² D1/8/15 and 6 mg/m² D1/8, ORR did not differentiate them; safety favored 6 mg/m² D1/8 as its predicted AE probabilities were mostly lower. For AEs favoring 6 mg/m² D1/8, predicted probabilities were lower by 0.1% – 15.5% as monotherapy and by 0.1% – 19.1% in combination. The utility score analysis favored 6 mg/m² D1/8 consistently for zele combined with P and remained neutral between the dosages for monotherapy. **Conclusions:** 6 mg/m² D1/8 was identified as the optimized zele dosage for monotherapy and in combination with P based on the overall benefit-risk informed by the comprehensive quantitative analyses. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

Avelumab + sacituzumab govitecan (Ave + SG) vs avelumab monotherapy (Ave mono) as first-line (1L) maintenance treatment for advanced urothelial carcinoma (aUC): Updated subgroup analyses of JAVELIN Bladder Medley based on metastatic sites.

Petros Grivas, Begoña P. Valderrama, Marinos Tsiatas, Peter Mu-Hsin Chang, Miso Kim, Lorenzo Antonuzzo, Sang Joon Shin, Georgios Gakis, Normand Blais, Se Hyun Kim, Jose Angel Arranz Arija, Harvey Yu-Li Su, Flora Zagouri, Marco Maruzzo, Astrid Schneider, Karin Tyroller, Jason Hoffman, Natalia Jacob, Jeannie Hoffman-Censits; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Hospital Universitario Virgen del Rocío, Sevilla, Spain; Athens Medical Center, Marousi, Greece; Taipei Veterans General Hospital, and Institute of Biopharmaceutical Science, National Yang Ming Chiao Tung University, Taipei, Taiwan; Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; Careggi University Hospital, Florence, Italy, & University of Florence, Florence, Italy; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Martin-Luther-University of Halle-Wittenberg, Halle, Germany; Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada; Seoul National University Bundang Hospital, Seongnam, South Korea; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; Alexandra Hospital, Athens, Greece; Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy; The Healthcare Business of Merck KGaA, Darmstadt, Germany; EMD Serono, Inc., Billerica, MA; EMD Serono, Billerica, MA; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Center, Baltimore, MD

Background: Ave 1L maintenance is a recommended treatment option for patients (pts) with aUC without progression after 1L platinum-based chemotherapy (PBC). In the JAVELIN Bladder Medley phase 2 trial (NCT05327530), 1L maintenance with Ave + SG (Trop-2-directed antibody-drug conjugate) improved progression-free survival (PFS) vs Ave mono (primary endpoint). In pts with aUC, presence of visceral metastases (including liver or lung) is associated with poorer prognosis. We report updated subgroup analyses from the primary analysis of JAVELIN Bladder Medley based on metastatic site. **Methods:** Pts with unresectable locally advanced or metastatic UC without progression after 4–6 cycles of 1L PBC were randomized 2:1 to receive Ave + SG or Ave mono, stratified by presence of visceral metastases at start of 1L PBC. Primary endpoints were investigator-assessed PFS (measured from randomization) and safety; overall survival (OS) was a secondary endpoint. For visceral and nonvisceral subgroups, PFS and OS data in the Ave mono arm were extended per protocol using propensity score-weighted data from the JAVELIN Bladder 100 phase 3 trial; extended data were not available for other subgroups. **Results:** At the start of 1L PBC, of 74 and 37 pts in the Ave + SG and Ave mono arms, respectively, 37 (50.0%) and 19 (51.4%) had visceral metastases, 20 (27.0%) and 11 (29.7%) had lung metastases, 17 (23.0%) and 7 (18.9%) had liver metastases, 17 (23.0%) and 11 (29.7%) had bone metastases, and 26 (35.1%) and 11 (29.7%) had lymph node-only disease. At data cutoff (Apr 28, 2025), in the Ave + SG and Ave mono arms, respectively, median follow-up for PFS was 15.7 and 25.1 mo. Across all subgroups, PFS was prolonged with Ave + SG vs Ave mono (Table); OS analyses were immature. In the Ave + SG and Ave mono arms, respectively, grade ≥ 3 treatment-related adverse events occurred in 72.2% and 5.6% of pts with visceral metastases, 57.9% and 0% of pts with lung metastases, 82.4% and 0% of pts with liver metastases, 82.4% and 0% of pts with bone metastases, 70.3% and 5.6% of pts with nonvisceral metastases, and 76.9% and 9.1% of pts with lymph node-only metastases. **Conclusions:** In the primary analysis of JAVELIN Bladder Medley, Ave + SG as 1L maintenance improved PFS vs Ave mono, irrespective of metastatic site. Clinical trial information: NCT05327530. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	PFS, median (95% CI), mo		HR (95% CI)
	Ave + SG	Ave mono	
Site of metastases at start of 1L PBC			
Visceral*	9.03 (5.62-13.80)	2.20 (1.91-3.71)	0.49 (0.28-0.84)
Nonvisceral	14.69 (7.43-NE)	7.33 (4.21-11.10)	0.61 (0.33-1.13)
Lung	8.77 (4.17-9.46)	1.81 (0.07-9.26)	0.43 (0.17-1.09)
Liver	8.77 (5.55-9.36)	2.69 (1.91-NE)	0.48 (0.17-1.32)
Bone	9.26 (5.49-17.64)	2.33 (0.07-5.45)	0.40 (0.16-0.99)
Lymph node only	14.00 (7.43-NE)	7.59 (1.87-NE)	0.65 (0.26-1.66)

*Pts could have ≥ 1 site of visceral metastases. HR, hazard ratio; NE, not estimable.

Longitudinal tumor-informed ctDNA monitoring and clinical outcomes in advanced urothelial carcinoma treated with enfortumab vedotin ± pembrolizumab.

Adanma Ayanambakkam, Kevin R. Reyes, Ryan Zhu, Cameron Herberts, Punashi Dutta, Ashley Wray, Beaux Mitchell, Syed Saqib Balkhi, Xiaolin Zhu, Carissa E. Chu, Sima P. Porten, Terence W. Friedlander, Jonathan Chou, Steven Neema Seyedin, Shruti Sharma, Meenakshi Malhotra, Minetta C. Liu, Adam ElNaggar, Vadim S. Koshkin; Stephenson Cancer Center, University of Oklahoma Health Sciences, Oklahoma City, OK; University of California San Francisco, San Francisco, CA; Natera, Inc., Austin, TX

Background: Enfortumab vedotin plus pembrolizumab (EV±P) is standard-of-care for patients (pts) with locally advanced/metastatic urothelial carcinoma (la/mUC), although not all pts experience durable benefit. Tumor-informed circulating tumor DNA (ctDNA) assays enable a personalized, real-time assessment of disease kinetics, and early ctDNA dynamics (<12 weeks) have been linked to EV±P radiographic response and survival outcomes. However, the prognostic relevance of ctDNA dynamics relative to durable clinical benefit is not well defined. **Methods:** We conducted a multicenter, retrospective real-world analysis of pts with la/mUC who received ≥1 cycle of EV±P and ≥1 commercial plasma ctDNA test using a clinically validated, personalized, tumor-informed assay (Signatera, Natera, Inc.). Associations between ctDNA features and progression-free survival (PFS) and overall survival (OS) were evaluated using Cox proportional hazards models. **Results:** A total of 110 pts with 545 plasma samples were analyzed. All pts had ≥1 ctDNA test (median: 4 tests/pt) immediately prior to and/or after EV±P initiation, with median time between serial ctDNA collections of 7.3 (IQR: 5.4–12.0) weeks. In this cohort, 69% (76/110) of pts had ≥1 ctDNA test (355 total) beyond 12 weeks post-EV±P initiation. Among these 76 pts, 31.5% (24/76) were persistently ctDNA negative (≥2 consecutively negative samples with no positives), while 65.8% (50/76) were anytime ctDNA-positive. Time-varying covariate analysis incorporating all serial results after 12-weeks reaffirmed that ctDNA-positivity was associated with worse PFS and OS (PFS: HR: 36.8, $p < 0.005$; OS: HR: 17.7, $p = 0.01$). Serial ctDNA negativity within 4–24 weeks (i.e. ≥2 consecutively negative samples with no positives) was strongly associated with durable OS/PFS beyond 24 weeks (PFS: HR=0.05, 95% CI: 0.01–0.42, $p = 0.005$; OS: HR=0.046, 95% CI: 0.0004–0.33 [Firth], $p = 0.0002$). Furthermore, single-timepoint ctDNA positivity evaluated at 12–24 weeks (HR: 11.8; 95% CI: 2.72–51.60; $p = 0.001$) and >24 weeks (HR: 6.8; 95% CI: 2.5–18.6; $p = 0.0002$) was strongly associated with inferior PFS. Findings were similar for OS (12–24wk: HR: 7.2, 95% CI: 1.7–31.3; $p = 0.008$; >24wk: HR=3.8, CI: 1.2–12.3; $p = 0.03$). **Conclusions:** Longitudinal ctDNA dynamics are strongly prognostic in pts with la/mUC treated with EV±P, even when assessed beyond 12 weeks from treatment start. Sustained ctDNA negativity further identifies pts with durable clinical benefit. These findings support ctDNA as a potentially complementary biomarker to standard imaging in this clinical context. Research Sponsor: None.

Untreated advanced urothelial carcinoma (aUC) in the modern treatment era: Patterns of care from a decade-long national cohort.

Melanie Mayer, Nicholas Seewald, Aram Babcock, Blanca Homet Moreno, Chethan Ramamurthy, Haojie Li, Ronac Mamtani; Department of Biostatistics, Epidemiology, & Informatics, University of Pennsylvania, Philadelphia, PA; Merck & Co., Inc., Rahway, NJ; Division of Hematology and Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: Over the past decade, the therapeutic landscape for locally advanced/unresectable and de novo metastatic urothelial cancer (aUC) has transformed with the introduction of immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs). These agents offer a more favorable benefit-risk and superior efficacy vs historical chemotherapy. We hypothesized that the proportion of untreated patients with aUC has declined over time, reflecting increased uptake of novel therapeutics. **Methods:** We analyzed the U.S. Flatiron Health EHR-derived de-identified database. We included patients diagnosed with aUC between Jan 1, 2011 and April 30, 2025. Patients were classified as treated if they received first-line (1L) systemic therapy within 6 months of advanced diagnosis. Calendar time was divided into three clinically relevant eras: pre-ICI approval (2011–2016), post-ICI but pre-ADC approval (2017–2019), and post-ADC approval (2020–2025). Outcomes included proportion untreated and time to treatment initiation (TTI) from advanced diagnosis. We estimated the cumulative incidence of treatment initiation using competing-risk methods, treating death before initiating as a competing event. Subgroup analyses evaluated patients with de novo stage IV disease at initial diagnosis. **Results:** We identified 12,849 patients with aUC (median age 73, 72.9% male, 78.7% white, 57.5% cis-ineligible, 78.3% bladder primary site). The proportion remaining untreated 6 months post advanced diagnosis declined across therapeutic eras: 36.8% untreated in the pre-ICI era, 27.4% in the post-ICI, pre-ADC era, and 22.7% untreated in the post-ADC era. Year-specific analysis showed steady improvement in treatment uptake: treatment within 6 months rose from 56% in 2011 to 79% in 2024 (Table). In the TTI analysis, overall, 25.1% had not initiated 1L therapy before death or data cutoff. Median TTI shortened across eras (63 days, 49 days, 45 days) and competing-risk cumulative incidence initiating therapy increased over time. For example, the probability of initiating 1L therapy within 90 days of aUC diagnosis across eras was 55.9% (pre-ICI), 66.1% (post-ICI, pre-ADC) and 70.7% (post ADC). **Conclusions:** In a large national cohort, untreated rates among patients with aUC declined markedly from 2011–2025 paralleling the introduction of ICIs and ADCs. Novel, better-tolerated therapies appear to have expanded real-world treatment eligibility and reduced early attrition. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Temporal trends in treatment rates.														
Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
3 months	0.48	0.53	0.54	0.57	0.58	0.61	0.68	0.65	0.67	0.69	0.69	0.72	0.7	0.74
6 months	0.56	0.6	0.61	0.63	0.65	0.69	0.73	0.7	0.74	0.76	0.76	0.78	0.78	0.79
1 year	0.58	0.63	0.64	0.66	0.67	0.71	0.75	0.72	0.77	0.77	0.77	0.79	0.8	0.81

Characterizing the immune effects of enfortumab vedotin and pembrolizumab (EV+P) on peripheral blood mononuclear cells (PBMCs) in metastatic urothelial cancer patients (mUC).

Aditi Gupta, Michal Sternschuss, Ashley M. Regazzi, Firas Ahmed, Samuel A. Funt, Gopa Iyer, Jonathan E. Rosenberg, Juan C. Osorio, David H. Aggen; Memorial Sloan Kettering, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Enfortumab vedotin improves response and outcomes over chemotherapy in mUC, with further benefit when combined with pembrolizumab. Although EV alone has limited immune-activating effects, we hypothesize that the combination of EV+P modulates peripheral T-cell activation states and correlates with clinical response. **Methods:** We conducted a retrospective analysis of mUC patients treated with EV+P at Memorial Sloan Kettering Cancer Center. PBMCs were isolated from patients on C1D1 and C2D1 of EV+P (n=33) and analyzed with a 32-color spectral flow cytometry panel. Immune subsets were compared between responders (complete [CR] or partial response [PR]) and non-responders (stable [SD] or progressive disease [PD]) using Wilcoxon rank sum test. Response was determined by a radiologist's assessment of the best-overall response on EV+P according to RECIST v1.1. **Results:** Among 33 patients, median age was 71 years and 48% were male. 12.1% (4/33) received prior platinum chemotherapy and 18.1% (6/33) received prior PD-1/PD-L1 immunotherapy. The objective response rate was 67% (CR=10; PR=12); eight patients had SD and three had PD. At C1D1, CD8+ T cell frequencies did not differ by response. At C2D1 however, circulating CD8+ T cells were significantly higher in non-responders ($p < 0.05$). From baseline to C2D1, CD8+ T cells showed increased expression of CTLA4+ ($p < 0.0001$), Ki67+ ($p < 0.01$) and HLA-DR+ ($p < 0.01$), with higher expression of each marker at C2D1 significantly correlated with response (all $p < 0.05$, Table 1). At C2D1, CD4+ effector T cells showed increased expression of Ki67+ and HLA-DR+ (both $p < 0.05$), both significantly higher in responders (both $p < 0.05$). CD4+ regulatory T cells showed increased CTLA4+ ($p < 0.001$), Ki67+ ($p < 0.01$) and HLA-DR+ ($p < 0.01$) expression from C1D1 to C2D1, with significantly higher expression in responders (CTLA4+ $p < 0.05$, Ki67+ $p < 0.0001$, HLA-DR+ $p < 0.001$). Across all T cell subtypes, PD1+ expression significantly decreased ($p < 0.05$) from C1D1 to C2D1, but this decrease did not correlate with response. The frequencies of circulating memory CD8+ and CD4+ T cells did not change on treatment or correlate with response at either timepoint. **Conclusions:** EV+P induces early peripheral T cell activation in mUC, with increased expression of activation and proliferative markers in responders at C2D1. Ongoing studies are investigating correlation between TCR specificity, immune activation and responses to EV+P. Research Sponsor: Bladder Cancer Advocacy Network.

Peripheral CD8+ T cell frequencies (median) at C1D1 and C2D1 from mUC patients on EV+P.

CD8+ T Cell	C1D1	C2D1	p-value	C2D1 in Responders	C2D1 in Non-Responders	p-value
CD8+ (%CD45+)	8.54	7.8	0.6	7.27	13.8	0.03
CTLA4+ (%CD8+)	1.15	3.94	0.0001	4.57	2.85	0.02
Ki67+ (%CD8+)	3.18	6.27	0.005	7.26	5.4	0.04
HLA-DR+ (%CD8+)	4.66	9.37	0.004	10.22	4.13	0.04
PD-1+ (%CD8+)	45.6	29.8	0.0005	28.7	31.5	0.48

Genomic determinants of metastatic burden and survival in metastatic urothelial carcinoma.

Milit S. Patel, James Robert Janopaul-Naylor, Shivaek Venkateswaran, Rohit Mantena, Sruthi Ranganathan, Alessandro Hammond, Yue Helen Zhang, Jonas Willmann, Edward Christopher Dee, Himanshu Nagar, Puneeth Iyengar; The University of Texas at Austin, Austin, TX; University of Pennsylvania, Philadelphia, PA; Memorial Sloan Kettering Cancer Center, New York, NY; University of Cambridge, Cambridge, United Kingdom; Harvard University, Cambridge, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Metastatic urothelial carcinoma (mUC) has variable outcomes. Metastatic site count (MSC) correlates with prognosis; the genomic landscape underlying metastatic burden and survival is poorly characterized. We investigated associations among somatic alterations, metastatic patterns, and survival in a large clinical-genomic cohort. **Methods:** We analyzed 1,157 patients with metastatic bladder cancer by integrating genomic data from the AACR Project GENIE Cohort v18.0—public with clinical annotations and metastatic site information from the MSK-MET database. Associations between 428 genomic alterations and MSC were assessed using Mann-Whitney tests. Survival analyses (n=1,153; 364 events) used Kaplan-Meier estimation, log-rank tests, and Cox regression. Models were adjusted for age, MSC (stratified), and location (lymph, liver, lung). FDR correction was applied, and proportional hazards assumptions verified. **Results:** Median age was 68.7 years; median OS was 15.8 months. MSC stratification revealed survival differences: 0–1 sites (n=515, median OS not reached), 2–4 sites (n=415, median OS 62.8 months), and ≥5 sites (n=223, median OS 13.1 months; log-rank $p < 2.5 \times 10^{-19}$). Each increase in MSC category was associated with worse OS (FDR $p < 0.001$). MSC predicted 2-year survival with an AUC of 0.78 (95% CI: 0.75–0.82). Six alterations were significantly associated with lower MSC (FDR < 0.05): *ERCC2* (n=122; d=0.50, FDR $p=5.6 \times 10^{-6}$), *STAG2* (n=128; d=0.40, FDR $p=1.9 \times 10^{-4}$), *FBXW7* (n=96; d=0.36, FDR $p=7.1 \times 10^{-3}$), *FGFR3* (n=291; d=0.17, FDR $p=8.1 \times 10^{-3}$), *TP53BP1* (n=35; d=0.59, FDR $p=4.3 \times 10^{-2}$), and *ARID2* (n=70; d=0.41, FDR $p=4.6 \times 10^{-2}$). *ERCC2* mutation frequency was 15.7% in 0–1 sites and 4.0% in ≥5 sites. Conversely, *CDKN2A/B* deletions were enriched in patients with ≥5 sites (28.3%/27.9%) compared with 0–1 sites (16.5%/15.9%; FDR $p < 0.01$). Five alterations were independently associated with OS in univariable analysis (FDR < 0.05): *CDKN2B* deletion (HR 1.81, 95% CI: 1.43–2.28, FDR $p=1.7 \times 10^{-4}$), *CDKN2A* deletion (HR 1.79, 95% CI: 1.42–2.26, FDR $p=1.7 \times 10^{-4}$), *ERCC2* mutation (HR 0.39, 95% CI: 0.24–0.62, FDR $p=1.1 \times 10^{-2}$), *CREBBP* mutation (HR 0.53, 95% CI: 0.37–0.75, FDR $p=3.1 \times 10^{-2}$), and *KDM6A* mutation (HR 0.66, 95% CI: 0.52–0.84, FDR $p=4.4 \times 10^{-2}$). In multivariable analysis adjusting for age, MSC, and location, no genomic alterations retained independent significance, suggesting MSC mediates these prognostic effects. Penalized regression confirmed MSC as the dominant prognostic variable (HR 1.39 per site increase). **Conclusions:** DNA damage repair and chromatin modifier mutations are associated with oligometastatic phenotypes and favorable survival, whereas *CDKN2A/B* deletions correlate with polymetastatic disease. The attenuation of genomic effects after MSC adjustment suggests that metastatic burden is a key mediator. These findings support using genomic profiling to guide mUC prognosis. Research Sponsor: Prostate Cancer Foundation; National Cancer Institute; P30 CA008748.

CXCL9:SPP1 ratio: Macrophage polarization and outcomes with pembrolizumab or enfortumab vedotin plus pembrolizumab in metastatic urothelial cancer.

Saad Omar Atiq, Tolulope Tosin Adeyelu, Sudeh Izadmehr, Jonathan F. Anker, Eric James Miller, Teja Ganta, Bobby Chi-Hung Liaw, Stephen Phillip Bohlman, Alexander B. Karol, Byuri Angela Cho, Andrew Elliott, Pedro C. Barata, Rana R. McKay, Reza Mehrazin, Amir Horowitz, John Sfakianos, Nina Bhardwaj, Matthew D. Galsky; Mount Sinai Tisch Cancer Center, New York, NY; Caris Life Sciences, Phoenix, AZ; Icahn School of Medicine at Mount Sinai, New York, NY; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Mount Sinai Medical Center, Tisch Cancer Institute, New York, NY; Mount Sinai Tisch Cancer Center, New York, NY; Genomic Medicine Institute, Medical Research Center, Seoul National University, Seoul, South Korea; Department of Medicine, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; UC San Diego Moores Cancer Center, La Jolla, CA; Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai, New York, NY; Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Enfortumab vedotin plus pembrolizumab (EV+P) is standard first-line treatment for metastatic urothelial cancer (mUC), yet responses vary considerably. Identifying resistance mechanisms may guide patient selection and inform novel therapeutic strategies. Single-cell RNA sequencing (RNA-Seq) across tumor types has revealed dichotomous tumor-associated macrophage (TAM) populations: SPP1+ TAMs exhibit tumor-promoting programs while CXCL9+ TAMs express programs associated with anti-tumor immunity. The CXCL9:SPP1 gene expression ratio (CS ratio) from bulk RNA-Seq captures this balance and correlates with outcomes across solid tumors (Bill et al, Science, 2023). We explored the CS ratio's association with outcomes in mUC patients receiving pembrolizumab monotherapy or EV+P. **Methods:** We retrospectively analyzed mUC patients who underwent molecular profiling at Caris Life Sciences using NGS (592-gene panel, DNA WES, or RNA WTS). CS ratios were calculated and patients stratified into quartiles (Q1–Q4; Q4=highest ratio). PD-L1 expression was assessed by IHC (22c3, positive (+) CPS $\geq$ 10%) while TMB-High was defined as $\geq$ 10 Mut/Mb. TME composition was inferred using quanTIseq. Real-world overall survival (rwOS) was derived from insurance claims and calculated from biopsy to last contact or time on treatment (TOT) using Kaplan-Meier analysis while Hazard ratio (HR) was calculated by Cox proportional hazard method. Mann-Whitney U and χ^2 /Fisher exact tests were applied with adjustment for multiple comparisons. **Results:** Among 6,708 mUC patients, 1,299 received pembrolizumab and 561 received EV+P. Lower CS ratios (SPP1+ TAM predominance) were associated with shorter time on treatment and rwOS (Table 1). Low CS ratio was also associated with reduced PD-L1 expression (15.5% vs 66.7%, $p < 0.001$) and TMB-H prevalence (34.6% vs 52.3%, $p = 0.006$). Low CS ratio tumors demonstrated reduced immune infiltration except for neutrophil enrichment. **Conclusions:** Lower CS ratios associate with shorter time on treatment and rwOS with both pembrolizumab and EV+P. To our knowledge, this is the first analysis linking macrophage transcriptional states with EV+P resistance. Further validation of the CS ratio in patients treated with EV + P or P is warranted. Research Sponsor: None.

CS ratio and associated outcomes with pembrolizumab monotherapy and EV+P.

CS Ratio	Pembrolizumab Monotherapy		EV + P	
	TOT (months)	OS (months)	TOT (months)	OS (months)
CS-Q1	2.7 (2.1-3.0)	5.7 (4.4-8.2)	7.6 (6.2-8.8)	17.8 (13.8-19.8)
CS-Q2	3.1 (2.2-4.1)	7.2 (5.4-8.8)	6.9 (6.0-8.0)	16.4 (13.2-19.4)
CS-Q3	4.5 (3.9-5.6)	13.5 (10.7-16.8)	9.2 (8.1-10.8)	17.2 (14.4-20.3)
CS-Q4	6.9 (4.9-8.7)	18.7 (13.1-23.7)	10.6 (9.3-12.2)	21.8 (16.5-28.1)
CS-Q4 vs. CS-Q1	HR 0.56, 95% CI 0.47-0.67, $p < 0.001$	HR 0.53, 95% CI 0.44-0.64, $p < 0.001$	HR 0.69, 95% CI 0.54-0.87, $p = 0.00189$	HR 0.62, 95% CI 0.46-0.83, $p = 0.00148$

The role of NECTIN4 in shaping the tumor microenvironment and potentiating the efficacy of immunotherapy in bladder cancer.

Kazuki Nishimura, Ryoichi Maenosono, Kensuke Hirotsuna, Takuya Tsujino, Mitsuki Ishida, Zyunko Zenko, Haruhito Azuma, Kazumasa Komura, Akihito Yoshimi; Harvard Medical School, Brigham and Women's Hospital, Boston, MA; Osaka Medical and Pharmaceutical University, Takatsuki, Japan; The University of Tokyo, Kashiwa, Japan; Department of Urology, Kawasaki University School of Medicine, Kurashiki, Okayama, Japan; National Cancer Center, Tokyo, Japan

Background: The EV-302 trial established enfortumab vedotin plus pembrolizumab (EV/P) as first-line therapy for metastatic urothelial carcinoma (UC). Although EV/P is administered without NECTIN4 testing based on the assumption of uniform NECTIN4 expression, real-world data have identified NECTIN4-low tumors associated with inferior responses to EV, highlighting the need for NECTIN4-based precision therapy. We aimed to define the molecular and immunologic roles of NECTIN4, identify predictive biomarkers of EV/P outcomes, and explore rational therapeutic strategies for NECTIN4-low UCs. **Methods:** We performed multi-omics analyses of 817 UC cases integrating whole-exome sequencing, RNA-seq, multiplex immunofluorescence, and spatial single-cell profiling (CODEX). We evaluated associations among NECTIN4 status, molecular subtype, tumor microenvironment (TME), survival, and response to immune checkpoint inhibitors. Basal bladder cancer (BC) cell lines and orthotopic MB49 bladder cancer models with NECTIN4 overexpression (OE) or control were used to assess tumor biology and therapeutic response. **Results:** Clustering by NECTIN4 H-score and molecular subtype revealed that basal/squamous (Ba/Sq) muscle-invasive BCs with low NECTIN4 had significantly worse survival outcomes than NECTIN4-high tumors in both our cohort ($P=0.001$) and the IMvigor210 trial ($P=0.019$). In vitro, NECTIN4 OE in basal BC cells suppressed proliferation and migration through downregulation of inflammation-related signaling pathways. CIBERSORTx and EcoTyper analysis of RNA-seq data indicated a more immune-inflamed TME in NECTIN4-high Ba/Sq tumors. Spatial single-cell profiling showed increased CD8+ T cells, particularly CD8+/TIGIT+ cells, in NECTIN4-high Ba/Sq UCs. Moreover, in orthotopic mouse models, NECTIN4-OE tumors exhibited reduced growth and increased CD8+ T-cell infiltration. Clinically, NECTIN4-high Ba/Sq tumors showed higher objective response rate (ORR) to pembrolizumab/avelumab than NECTIN4-low tumors (55.5% vs 0%, $P=0.002$) in our cohort; in IMvigor210, NECTIN4-high Ba/Sq patients also had superior ORR (38.5% vs 15.6%, $P=0.025$). Additionally, in orthotopic mouse models, EV/P showed limited efficacy in NECTIN4-low tumors, whereas NECTIN4-OE tumors responded well. Transcriptomic analyses identified histone deacetylases (HDAC) as potential targets in NECTIN4-low tumors; accordingly, HDAC inhibitors demonstrated greater efficacy in NECTIN4-low basal BCs in vitro and vivo. **Conclusions:** NECTIN4 influences tumor progression and shapes the TME, thereby impacting immunotherapy efficacy. NECTIN4 is a potential predictive biomarker for survival and for outcomes with immunotherapy and EV/P in Ba/Sq UCs. NECTIN4-low Ba/Sq tumors may require alternative strategies, and HDAC inhibition represents a rational therapeutic approach for NECTIN4-low Ba/Sq UC patients. Research Sponsor: None.

Outcomes with first-line (1L) platinum-based chemotherapy (PBC) and avelumab 1L maintenance in locally advanced or metastatic urothelial carcinoma (la/mUC) by *NECTIN4* and *HER2* RNA expression: Exploratory analyses from JAVELIN Bladder 100.

Niklas Klümper, Markus Eckstein, Petros Grivas, Enrique Grande, Johannes Brägelmann, Olga Bogatyrova, Jason Hoffman, Viktor Grünwald; University Hospital Bonn, Bonn, Germany; University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Department of Medical Oncology, Quironsalud Madrid, Madrid, Spain; University of Cologne and University Hospital Cologne, Cologne, Germany; The Healthcare Business of Merck KGaA, Darmstadt, Germany; EMD Serono, Billerica, MA; Essen University Hospital, Essen, Germany

Background: Nectin-4 and HER2 are relevant therapeutic targets and potential biomarkers for the treatment of la/mUC. *NECTIN4* and *HER2* RNA expression are heterogeneous in UC tumors, with highest expression observed in luminal molecular subtypes. We report exploratory biomarker analyses from the JAVELIN Bladder 100 phase 3 trial evaluating response to 1L PBC and survival outcomes with avelumab administered as 1L maintenance treatment in subgroups defined by tumor *NECTIN4* and *HER2* RNA expression. **Methods:** In JAVELIN Bladder 100 (NCT02603432), patients (pts) with unresectable la/mUC without progression after 4–6 cycles of 1L PBC were randomized 1:1 to receive avelumab + best supportive care (BSC) or BSC alone. Biomarker analyses were performed using existing whole transcriptome profiles generated using RNA sequencing, and transcript levels were quantified using Personalis ACE technology. *NECTIN4* and *HER2* RNA expression were assessed as continuous variables for subgroups defined by response to 1L PBC and as dichotomous variables (median and lower quartile split) for stratified survival analyses. **Results:** In biomarker-assessable pts (n=560) who had complete response (CR; n=149), partial response (n=261), or stable disease (SD; n=150) to 1L PBC, no significant differences in tumor *NECTIN4* RNA expression were observed, whereas slightly higher tumor *HER2* RNA expression was observed in pts who had CR vs SD. Overall, when defined by median split, 201 pts (35.9%) had high *NECTIN4*/high *HER2* RNA expression, 202 (36.1%) had low *NECTIN4*/low *HER2*, 78 (13.9%) had high *NECTIN4*/low *HER2*, and 79 (14.1%) had low *NECTIN4*/high *HER2*. Molecular subtype was non-luminal in 20.4%, 87.1%, 55.1%, and 50.6%, respectively. The table shows overall survival (OS) with avelumab + BSC vs BSC alone in subgroups defined by combined high or low *NECTIN4*/*HER2* expression. OS improvements with avelumab + BSC vs BSC alone were observed across subgroups defined by high or low *NECTIN4*/*HER2* RNA expression alone. **Conclusions:** Exploratory analyses from JAVELIN Bladder 100 showed that pts with low *NECTIN4* and low or high *HER2* RNA expression had pronounced OS with avelumab 1L maintenance vs BSC alone. Results are hypothesis generating. Clinical trial information: NCT02603432. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	Avelumab + BSC	BSC
High <i>NECTIN4</i> /high <i>HER2</i>	n=100	n=101
Median OS (95% CI), mo	23.0 (17.8-30.9)	14.3 (10.8-21.3)
HR (95% CI)	0.73 (0.52-1.02)	
Low <i>NECTIN4</i> /low <i>HER2</i>	n=105	n=97
Median OS (95% CI), mo	29.8 (20.1-46.9)	18.8 (13.9-29.4)
HR (95% CI)	0.78 (0.55-1.11)	
High <i>NECTIN4</i> /low <i>HER2</i>	n=39	n=39
Median OS (95% CI), mo	18.4 (13.0-NE)	17.4 (14.0-NE)
HR (95% CI)	0.84 (0.47-1.50)	
Low <i>NECTIN4</i> /high <i>HER2</i>	n=40	n=39
Median OS (95% CI), mo	31.1 (20.6-NE)	15.8 (9.3-41.9)
HR (95% CI)	0.66 (0.38-1.15)	

Stratified subgroups defined by median split are shown. HR, hazard ratio; mo, months; NE, not estimable.

Treatment-free survival (TFS) in patients with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin (EV)–based therapy.

Salvador Jaime-Casas, Koral U. Shah, George Zhang, Jadon Fann, Vitor Abreu De Goes, Miguel Zugman, Ali Moradi, Nicholas Salgia, Daniela V. Castro, Benjamin Mercier, Nazli Dizman, Joann Hsu, Wesley Yip, Xiaochen Li, Alexander Chehrazi-Raffle, Sumanta Kumar Pal, Abhishek Tripathi; City of Hope Comprehensive Cancer Center, Duarte, CA; Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: EV as monotherapy or with pembrolizumab (EVP) has shown robust efficacy in patients with aUC. Despite lack of data, treatment breaks (TB) with EV are frequently utilized due to toxicity or patient/physician preference. In this retrospective real-world analysis, we evaluated TFS after temporary or permanent EV discontinuation in patients with aUC. **Methods:** A multicenter cohort of patients with aUC treated with EV/EVP between 01/2015 through 12/2025 were included. Patients were categorized in groups with or without TB (defined as ≥ 6 weeks between EV doses without progression). Baseline characteristics were summarized using descriptive statistics, and comparison was performed using the chi-square test/Fisher's exact and t-test, as appropriate. TFS was estimated using the Kaplan–Meier method among TB+ patients. Overall survival (OS) and progression-free survival (PFS) were estimated for both cohorts using the Kaplan–Meier method and compared using the log-rank test. Univariable and multivariable models adjusted for baseline variables evaluated factors associated with TFS, OS and PFS. **Results:** From a total of 172 patients eligible for inclusion, 25 (14%) received TB and 148 (86%) did not. Median age was 72.5 years. Most patients were White (76.3%), had primary bladder cancer (89%), and received EVP (63%). Overall, 30% had ≥ 1 prior line of therapy. Baseline characteristics did not differ significantly between patients with and without TB. Most common reason for TB was treatment toxicity (52%) and a minority (20%) continued pembrolizumab during their break. The median TFS was 3.6 months (95% CI 3.0, 8.3), with 28% experiencing a TFS ≥ 24 weeks. TB did not compromise outcomes, and patients with a TB demonstrated longer median PFS (13.5 vs. 7.7 months, $p=0.05$) and OS (not reached vs 21.8 months, $p=0.008$). Prior radiation therapy (OR 0.18 (95% CI 0.06–0.53, $p=0.002$) and prior adjuvant chemoimmunotherapy (OR 0.18 (95% CI 0.04–0.77, $p=0.02$) were independently associated with decreased odds of experiencing a TB. **Conclusions:** Treatment break on EV therapy did not compromise outcomes and resulted in TFS lasting ≥ 6 months in a subset of patients. Rational treatment de-escalation strategies in selected patients need to be prospectively investigated to mitigate long-term toxicity in patients with aUC undergoing EV-based therapy. Research Sponsor: None.

Quantitative pre-cystectomy ctDNA levels for identification of ctDNA-positive patients with surgically curable loco-regional disease versus those with occult micrometastatic progression.

Ruveyda Ayasun, Eric James Miller, Lexi S. Weintraub, Lydia Wu, Anna Argulian, Annabelle Elikan, Thomas Joseph Otten, Erin Heath, Teja Ganta, Saad Omar Atiq, Jonathan F. Anker, Marcio A. Diniz, Matthew D. Galsky, Alexander B. Karol; Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; Mount Sinai Tisch Cancer Center, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Mount Sinai Tisch Cancer Center, New York, NY

Background: Radical cystectomy (RC) is a life-altering operation associated with substantial morbidity. Despite its curative intent for muscle-invasive urothelial carcinoma (MIUC), approximately 50% of patients experience metastatic recurrence after surgery. Identifying patients destined to relapse despite RC could help spare them from the morbidity of surgery and instead direct them toward alternative systemic therapies. While ctDNA-positive assays post-neoadjuvant therapy (NAT) but pre-cystectomy are associated with a poor prognosis, a subset of patients with ctDNA positive assays pre-cystectomy “clear” ctDNA with cystectomy alone (Powles, ASCO, 2025). We hypothesized that quantitative pre-cystectomy ctDNA thresholds may therefore distinguish local, surgically curable, bladder cancer versus micrometastatic disease. **Methods:** We conducted a retrospective single-institution cohort study of patients undergoing RC who had tumor-informed ctDNA (Signatera) assays ≤ 60 days pre-surgery and within ± 30 days of a 3-month postoperative landmark. The primary outcome was ctDNA positivity at this landmark. The analyses proceeded in two steps: (1) association between log-transformed pre-cystectomy ctDNA and 3-month ctDNA positivity, assessed using logistic regression; and (2) derivation of the maximal quantitative preoperative ctDNA threshold > 0.02 Mean Tumor Molecules per Milliliter (MTM/ml) using constrained optimization (target sensitivity $\geq 80\%$, specificity $\geq 50\%$), with internal validation via Efron-Gong bootstrap resampling. **Results:** Of 45 patients with MIUC meeting inclusion criteria, 10 (22.2%) received NAT. Higher pre-cystectomy ctDNA correlated with ctDNA positivity at the post-cystectomy landmark timepoint (odds ratio per 10-fold increase 1.6, 95% CI 1.2–2.4; $p < 0.01$). A pre-cystectomy ctDNA threshold ≥ 0.06 MTM/ml (95% CI 0.04–2.475) demonstrated optimal performance characteristics and was confirmed on bootstrap validation (sensitivity 81.6% [95% CI 61.1–88.9%], specificity 66.4% [95% CI 51.9–96.3%], positive predictive value [PPV] 63.8% [95% CI 55.2–91.7%], and negative predictive value [NPV] 85.1% [95% CI 78.8–88.9%]). **Conclusions:** Higher pre-cystectomy ctDNA values correlate with a higher likelihood of a persistent ctDNA-positive assay at 3 months post-cystectomy. In this dataset, a ctDNA threshold of ≥ 0.06 MTM/ml identified patients with high sensitivity and NPV for post-operative micrometastatic disease. Further validation of these findings, and threshold, in larger cohorts (with or without NAT) are needed to refine MIUC care by testing strategies involving (alternative) NAT versus proceeding with cystectomy. Research Sponsor: The Mount Sinai Hospital.

Outcomes with enfortumab vedotin (EV) rechallenge after disease progression in metastatic urothelial carcinoma.

Michal Sternschuss, Alyssa Arbuisa, Eric Huttenlocher Bent, Aditi Gupta, Ashley M. Regazzi, Stanley Liang, Allen Mena, Scot Anthony Niglio, Daniel E. Lage, Samuel A. Funt, Gopa Iyer, David H. Aggen, Jonathan E. Rosenberg; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering, New York, NY; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: EV, alone (mono) or with pembrolizumab (EVP), is an established therapy for metastatic urothelial carcinoma (mUC). However, the activity with EV rechallenge after prior exposure and subsequent disease progression is not well defined. **Methods:** A retrospective institutional database of patients (pts) treated with EV mono (n=395) or EVP (n=256) for mUC was reviewed to identify pts who received EV rechallenge after disease progression. EV-free interval (EVFI) was defined as the time from last EV1 (initial) dose to first EV2 (rechallenge) dose. Investigator-assessed objective response rate (ORR; CR/PR), progression free survival (PFS), overall survival (OS), and duration of response (DoR, from first documented response) were summarized descriptively. **Results:** Of 42 pts identified, EV1 regimen was mono for 62% (n=26; EV1-mono) and EVP for 38% (n=16; EVP1). Median age was 77, 76% were male, and 45% had upper tract primary. Most pts (n=35; 83%) discontinued EV1 for toxicity, predominantly peripheral neuropathy. Median follow up from EV2 initiation was 26 mo (95% CI 17–NR). At rechallenge, 10 pts (24%) switched EV regimens (EV1-mono to EVP2, n=5; EVP1 to EV2-mono, n=5). EV2 was initiated at 1.25 mg/kg in four pts (9.5%), 1.0 mg/kg in 13 pts (31%), and ≤0.75 mg/kg in 25 pts (60%). Among response-evaluable pts (n=39), ORR to EV2 was 21% (8/39; 95% CI 9%–36%), including 2 CRs (5%), both with prior CR to EV1. No responses were observed in pts with SD/PD to EV1 (0/8; 0%), or those with EV1 PFS <6 mo (0/11; 0%). Among pts with long (>12 mo) or intermediate (6–12 mo) EVFI, ORR to EV2 was 33% (4/12) and 31% (4/13), respectively. No responses were reported with short (<6 mo) EVFI (0/14; 0%). EV2 was initiated at 0.75 mg/kg in 5/8 pts with CR/PR. Median PFS and OS estimated from EV2 start were 2.8 and 18.5 mo. Among pts with CR/PR, median DoR was 7.0 mo (95% CI 3.5–NR). At last follow up, three pts remained on EV2; 39 pts discontinued EV2 due to progression (74%, n=29), toxicity (23%, n=9) or pt preference (2.6%, n=1). **Conclusions:** In a real-world cohort, EV rechallenge demonstrated modest activity, primarily in pts with prior benefit from EV and EVFI >6 mo. These observations underscore the need for further studies to clarify the effects of repeated EV exposure and optimize patient selection. This is particularly relevant given efforts to mitigate toxicity and the emerging issue of recurrent disease after perioperative EVP. Research Sponsor: National Cancer Institute; P30 CA008748; U.S. National Institutes of Health; P50 CA221745.

	All N = 42	EV1-mono N = 26	EVP1 N = 16
EV1			
ORR (95% CI)	79% (63%–90%)	85% (65%–96%)	69% (41%–89%)
Median PFS, mo (95% CI)	8.3 (7.5–9.9)	8.6 (7.7–19.1)	7.6 (5.5–11.9)
Median Time on EV, mo [IQR]	4.9 [3.7–7.2]	5.1 [4.1–8.7]	4.1 [2.4–5.7]
EV2			
ORR (95% CI)	8/39; 21% (9%–36%)	5/25; 20% (7%–41%)	3/14; 21% (5%–51%)
NE	3	1	2
Median PFS, mo (95% CI)	2.8 (2.6–5.1)	2.7 (2.6–5.3)	4.1 (2.6–NR)
Median OS, mo (95% CI)	18.5 (11.6–29.7)	18.5 (11.0–29.7)	15.2 (12.6–NR)
Median Time on EV, mo [IQR]	2.8 [1.9–5.6]	2.5 [1.9–5.1]	3.4 [1.9–6.1]

A phase 1b study of SYS6002 in advanced solid tumors.

Yao Zhu, Dingwei Ye, Jian Zhang, Shanshan Wang, Xin Yao, Qiang Lv, Yuping Sun, Tongsen Zheng, Ming Liu, Guiling Li, Wei Li, Funan Liu, Jinsheng Shi, Xin An, Yongmei Yin, Jing Yuan, Ying Chen, Pan Shu, Jingyi Zhang, Jihao Zhang; Fudan University Shanghai Cancer Center, Shanghai, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Jiangsu Province Hospital, Nanjing, China; Cancer Hospital of Shandong First Medical University, Jinan, China; Harbin Medical University Cancer Hospital, Harbin, China; Beijing Hospital, Beijing, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; The First Hospital of Jilin University, Changchun, China; The First Affiliated Hospital of China Medical University, Shenyang, China; Cangzhou People's Hospital, Cangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; CSPC Pharmaceutical Group Co., Ltd., Shijiazhuang, China

Background: SYS6002 is a next-generation Nectin-4-targeting antibody-drug conjugate (ADC) utilizing a novel site-specific enzymatic conjugation technology to link monomethyl auristatin E (MMAE) with a uniform drug-antibody ratio of 2. This design aims to enhance linker stability, minimize free payload release, and improve the therapeutic window. **Methods:** This phase 1 study (ChiCTR2200066256) included dose escalation (0.2–4.5 mg/kg Q3W; 2.4–2.7 mg/kg Q2W), pharmacokinetic (PK) expansion, and cohort expansion phases. Eligible patients had advanced solid tumors refractory to standard therapies. The primary endpoints were safety and recommended phase 2 dose (RP2D). Secondary endpoints included PK profile and efficacy, with the latter reported herein were specific to the pretreated advanced urothelial carcinoma (aUC) cohort. **Results:** As of Dec 19, 2025, 150 patients were enrolled (dose escalation n=32; PK expansion n=70; cohort expansion n=48). The maximum tolerated dose was not reached up to 4.5 mg/kg. The RP2D in aUC patients was determined as 3.6 mg/kg Q3W. SYS6002 exhibited a manageable safety profile in all 150 patients. With a median follow-up of 11.5 months (IQR 6.5–15.5), 2 (1.3%) patients discontinued treatment due to treatment-related adverse events (TRAEs) and no TRAE led to death. The most common TRAEs were ocular disorders (e.g., corneal disorder, dry eye), which were predominantly Grade 1–2. While ocular events were frequent (consistent with on-target effects), they were reversible and effectively managed with prophylaxis, resulting in no treatment discontinuations due to ocular toxicity. Notably, TRAEs typically associated with payload shedding were characterized by low incidence, with peripheral neuropathy reported in 11.3% of patients (no Grade ≥ 3) and rash in 20.7% (2.0% Grade ≥ 3), which compared favorably to historical data of other MMAE-based ADCs. Furthermore, no Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis reported. In 85 efficacy-evaluable aUC patients across all tested doses, the objective response rate (ORR) was 37.6% (95%CI 27.4–48.8) and disease control rate (DCR) was 77.6% (95%CI 67.3–86.0), with a median duration of response of 6.2 months (95%CI 4.3–10.4) and median overall survival of 13.2 months (95%CI 10.6–14.9). At the RP2D (n=39), the ORR reached 41.0% (95%CI 25.6–57.9). Encouragingly, in heavily pretreated patients with prior MMAE-based ADC exposure (n=25), SYS6002 maintained activity with an ORR of 24.0% (95%CI 9.4–45.1) and DCR of 72.0% (95%CI 50.6–87.9), suggesting potential to overcome resistance. **Conclusions:** SYS6002 demonstrated a distinct safety profile from other Nectin-4 ADCs. Its promising efficacy in aUC patients, extending to those progressing on prior MMAE-based ADCs, supports further phase 3 trials. Clinical trial information: ChiCTR2200066256. Research Sponsor: CSPC Megalith Biopharmaceutical Co., Ltd.

Proteomic profiling of circulating tumor cells (CTCs) in metastatic urothelial cancer (mUC) as associated with upregulation of EGFR, HER2, and B7-H3 in patients (pts) progressing on enfortumab vedotin (EV) plus pembrolizumab.

Wadih Issa, Navneet Kaur, Qinhan Zhou, Ze Yu, Shahed Abdullah, Libin Yan, Chao Xing, Suzanne Cole, Changchuan Jiang, Qian Qin, Jue Wang, Kevin Dale Courtney, Andrew Zhuang Wang, Tian Zhang; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Eugene McDermott Center for Human Growth and Development, UT Southwestern Medical Center, Dallas, TX; UT Southwestern, Dallas, TX; Division of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Eugene McDermott Center for Human Growth and Development; Lyda Hill Department of Bioinformatics; O'Donnell School of Public Health, UT Southwestern Medical Center, Dallas, TX; Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, TX; Department of Internal Medicine, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX

Background: Pts with mUC have poor prognosis, and while EV/pembro have improved outcomes, therapeutic targets arising after EV-pembro treatment are elusive. Proteomic profiling of circulating tumor cells (CTCs) offer a minimally invasive approach to capture tumor biology changes in real-time. We evaluated CTC burden and proteomic changes in relation to treatment response in mUC. **Methods:** Pts with mUC were prospectively enrolled at UT Southwestern Medical Center. Peripheral blood samples were collected at baseline, 4 weeks, and 12 weeks of treatment, as well as progression of disease. CTCs were isolated using a dendrimer-based microfluidic chip assay functionalized with antibodies against EpCAM, Trop-2, Nectin-4, and FGFR3, identifying nucleated CTCs (DAPI+/CK+, CD45-). After CTCs were selected within regions of interest, spatial proteomic profiling was performed via the Nanostring GeoMx Immuno-Oncology Proteome Atlas panel. CTC variation and surface proteomics after treatment were primary objectives. CTC changes were considered concordant if they decreased >10% in pts with complete or partial response (CR or PR), remained stable (within 10% of baseline) in pts with stable disease (SD), or increased >10% in pts with progressive disease (PD), as defined by RECIST 1.1. One pt underwent post-treatment biopsy with IHC analysis. **Results:** Thirty pts with mUC were enrolled, with a median age of 71.5 years, predominantly male (26/30, 87%) and Caucasian (24/30, 80%). Most received EV/pembro (26/30, 86.7%), while the rest were treated with chemotherapy (3/30, 10%) or SG (1/30, 3%). Median CTC counts (cells/ml) were assessed at baseline (30.3, IQR 18.5–62.9), at week 4 (22.3, IQR 6.0–37.0), and at week 12 (29.5, IQR 15.2–44.5). Twenty-two pts had sufficient radiographic and clinical follow up. CTC changes were concordant with treatment responses in 77% (17/22) of pts, including 12/22 pts with CR/PR, 3/22 with SD, and 7/22 with PD. Proteomic profiling of serial CTCs from 9 pts treated with EV/pembro revealed dynamic proteomic changes from baseline to week 12 and at disease progression. Together, these pts demonstrated upregulation of activated EGFR (phospho-Y1068), HER2 (phospho-Y877), STAT5, FAK, and vimentin. Pts with primary PD (n=3) showed B7-H3 upregulation on CTCs, whereas pts with secondary PD (n=2) showed higher expression of vimentin, c-MET, and MHC class I on CTCs. IHC of a post-EV/pembro progression bone metastasis confirmed increased HER2 expression (2+). **Conclusions:** CTCs with proteomic profiling can serve as a dynamic, noninvasive biomarker in mUC, identifying distinct therapeutic targets for pts progressing on EV/pembro. The emergence of actionable pathways, including EGFR, HER2, c-MET, and B7-H3, suggests opportunities for rational, biomarker-driven therapeutic strategies. Research Sponsor: Cancer Prevention & Research Institute of Texas; RR210079.

Responses to trastuzumab deruxtecan (T-DXd) in HER2 IHC spectrum 2+ versus 3+ urothelial carcinoma across lines of therapy.

Sara El Sarout, Mahmut Akgul, Rashad Nawfal, Wassim Daoud Khatoun, Razane El Hajj Chehade, Tarek Baroud, Gunsagar Singh Gulati, Gabriella Rickards, Brady James, Gaelle Nafeh, Elio Ibrahim, Charlene Mantia, Toni K. Choueiri, Michelle S. Hirsch, Joaquim Bellmunt; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background: The role of HER2 as a therapeutically actionable target has been validated with the DESTINY-PanTumor02 trial demonstrating meaningful clinical benefit to T-DXd across HER2-expressing bladder malignancies leading to the FDA approval in the immunohistochemical (IHC) 3+ population. We explore the clinical outcome of real-world patients with urothelial carcinoma (UCa) on T-DXd and its correlation with molecular and pathological findings across all the HER-2 IHC scores (e.g., 0 to 3+). **Methods:** We reviewed the clinical, pathologic, and molecular data of 29 patients with UCa, who received T-DXd between April 2024 and November 2025. Baseline clinical variables included age, sex, ECOG performance status, visceral metastases, line of therapy, and HER2 IHC score (adapted from gastric cancer scoring). Available genomic data included tumor mutational burden (TMB ≥ 10 mut/Mb), ERBB2 amplification and mutation, DNA damage response (DDR), FGFR alterations, and microsatellite instability (MSI) status. Outcomes of interest included Objective Response Rate (ORR), Disease Control Rate (DCR), and progression-free survival (PFS) and overall survival (OS) which were estimated using Kaplan-Meier methods and compared across groups using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios. **Results:** Higher HER2 IHC scores were associated with greater clinical activity and higher ORR in IHC 2+ (n=7; 42.9; 95% CI = 9.9–81.6%) tumors and HER2 IHC 3+ (n=20; 55.0; 95% CI = 31.5–76.9%). However, no response was seen in HER2 IHC 1+ (n=2). Median duration of response was 15.6 months in HER2 IHC 2+ and 11.6 months in HER2 IHC 3+ (15/30 patients received T-DXd in ≥ 3 lines). PFS and OS appeared comparable between HER2 2+ and HER2 3+ tumors, with no statistically significant difference by log-rank test (p = 0.67, p = 0.79 respectively). Elevated TMB was observed in 6/12 cases. ERBB2 amplification was detected in 3/10 of cases and ERBB2 mutation in 5/13 of cases. Alterations in DDR related genes and FGFR were identified in patients 2/11 and 1/12 respectively, while MSI-H was not observed in any case. Responses were numerically higher when T-DXd was given in 2nd line (53.3%, 95% CI 26.6–78.7%) than in further lines (42.9%, 95% CI 17.7–71.1%) and so was DCR 93% (95% CI 68.1–99.8%) in 2nd line than 71.4% (95% CI 41–91.6%) in further (≥ 3) lines. **Conclusions:** T-DXd demonstrated meaningful clinical activity not only in IHC 3+ but in IHC 2+ tumors as well, which is consistent with the results of the DESTINY-PanTumor02 trial. In this limited sample size, there was no statistically significant association between genomic features and patient outcomes. Larger studies are needed to further find predictors across different levels of IHC expression. Research Sponsor: None.

HER2 IHC Score	n	Responders (CR/PR)	ORR (%)	95% CI
1+	2	0	0.0	0.0–84.2%
2+	7	3	42.9	9.9–81.6%
3+	20	11	55.0	31.5–76.9%

Circulating tumor DNA (ctDNA) dynamics as early biomarkers of response to enfortumab vedotin plus pembrolizumab (EVP) in advanced urothelial carcinoma (aUC).

Mohammad Jad Moussa, Emanuele Crupi, Zachariah Thomas, Amishi Yogesh Shah, Jianjun Gao, Sangeeta Goswami, Pavlos Msaouel, Cindy Y. Jiang, Andrew Johns, Michael Glover, Nizar M. Tannir, Arlene O. Siefker-Radtke, Matthew T. Campbell, Omar Alhalabi; Internal Medicine Residency Program, Baylor College of Medicine, Houston, TX; Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Radiographic assessment of treatment response remains challenging in aUC. ctDNA testing offers a sensitive, noninvasive measure of real-time treatment response. With EVP established as a frontline standard, we hypothesized that ctDNA dynamics correlate with radiographic response and survival. **Methods:** We retrospectively analyzed an institutional cohort of 302 patients (pts) with aUC treated with EVP at MD Anderson; 79 pts with baseline and serial ctDNA testing using a tumor-informed assay (Signatera) (08/23–01/26) were included. ctDNA dynamics were evaluated in two ways: (1) early on-treatment change (baseline vs. first on-treatment ctDNA) for association with radiographic response, and (2) time-dependent modeling as a covariate in Cox proportional hazards analyses of progression-free survival (PFS) and overall survival (OS) to account for immortal-time bias. **Results:** All pts had a median of 4 ctDNA tests (range: 1–9). Baseline ctDNA was obtained before or at EVP start in 67 (84.8%). Among these patients, first ctDNA clearance occurred in 46.3%, decrease in 26.9%, and increase in 19.4%; 6% had persistently undetectable ctDNA and 1.5% was lost to follow-up. Median time to first ctDNA reduction (clearance or decrease) was 48 days [IQR: 40–86]. Pts without baseline ctDNA prior to EVP (12, 15.2%) were non-evaluable. The best overall response rate to EVP was 53/79 (67.1%), including complete in 13.9% and partial responses in 53.2%. Objective responses were highest among pts with first ctDNA clearance (87.1%), lower with first ctDNA decrease (55.6%), and uncommon with first ctDNA increase (38.4%) (χ^2 test, $p=0.003$). In the overall cohort ($n=79$), median PFS from EVP start was 20.4 months (mo) [95% CI: 8–NE] and median OS from EVP start was 30.3 mo [95% CI: 26.3–34.3], with a median follow-up of 12.1 mo [95% CI: 9.1–14.9]. In time-dependent Cox models accounting for immortal-time bias, increasing ctDNA levels over time were associated with inferior PFS (HR 1.49 [95% CI: 1.11–2]; $p=0.007$) and OS (HR 1.41, [95% CI: 0.96–2.08], $p=0.08$). **Conclusions:** Early ctDNA dynamics provide a clinically meaningful measure of response to EVP in aUC and correlate with imaging outcomes. ctDNA clearance identifies pts with deep and durable benefit, while lack of clearance flags early resistance. Longer follow-up will evaluate ctDNA-guided monitoring to inform treatment de-escalation or maintenance approaches. Research Sponsor: None.

Baseline characteristics of cohort ($n=79$).

Variable	Measure
Age at aUC diagnosis, median [IQR]	71 [65 – 76]
Sex, male, n (%)	56 (70.9%)
Tumor Origin, n (%)	
Bladder	61 (77.2%)
Upper Tract	18 (22.8%)
Visceral mets, n (%)	34 (43%)
Nodal-only mets, n (%)	40 (50.6%)
Baseline ctDNA before/at EVP start (MTM/mL), median [IQR]	
All ($n=67$)	12.9 [1.1 – 105.5]
Visceral mets ($n=30$)	12.8 [1.3 – 140.2]
Nodal-only mets ($n=33$)	16.9 [1.4 – 96]

Comparison of cisplatin/gemcitabine or carboplatin/gemcitabine on efficacy, toxicity, and quality of life from the randomized DISCUS trial.

Syed A. Hussain, Iciar García Carbonero, Javier Molina Cerrillo, Javier Puente, Pablo Borrega, Jahangeer Malik, Louis-Marie Dourthe, Robert Jones, Daniel Castellano, Yohann Lorient, Francesca Jackson-Spence, Garima Priyadarshini, Fahmida Jamal, Elizabeth Nally, Sara Coca Membribes, Charlotte Ackerman, Enrique Grande, Thomas Powles, Miguel A. Climent Duran; Division of Clinical Medicine, University of Sheffield, School of Medicine and Population Health, Sheffield, United Kingdom; Medical Oncology Department, Hospital Hospital Virgen de la Salud, Toledo, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Hospital Universitario Clínico San Carlos, Medical Oncology Department, Madrid, Spain; Hospital San Pedro de Alcántara, Cáceres, Spain; Edinburgh Cancer Centre, Western General Hospital, Edinburgh, United Kingdom; Department of medical oncology, Clinique Saint-Anne, Strasbourg, France; University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Hospital Universitario 12 de Octubre, Madrid, Spain; Université Paris-Saclay Gustave Roussy, Villejuif, France; Barts Cancer Institute, London, United Kingdom; Barts Cancer Institute, London, United Kingdom; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Facultad de Medicina, Universidad Francisco de Vitoria, Madrid, Spain; Barts Cancer Institute, NIHR Biomedical Research Centre, Queen Mary University of London, London, United Kingdom; Fundación Instituto Valenciano de Oncología, Valencia, Spain

Background: The DISCUS trial compared 3 versus 6 cycles (3C versus 6C) of chemotherapy followed by avelumab in 267 patients receiving first-line treatment for metastatic urothelial cancer. It showed 3 cycles of chemotherapy followed by maintenance avelumab was associated with better QoL than six cycles (NCT06892860). Efficacy outcomes of the two arms appeared similar. Here we compare the cisplatin (cis) or carboplatin (carbo) chemotherapy subsets in the 3C and 6C arms. **Methods:** Patients were randomized to receive either 3 or 6 cycles of chemotherapy. Cisplatin or carboplatin was allocated by physician choice. Progression free survival (PFS), Overall survival (OS), response rates, patient-reported outcomes (PROs) and treatment related adverse events were collected (TRAEs) were collected. The analysis was exploratory and p values nominal. **Results:** 267 were included of whom 55 received 3C/cis, 55 6C/cis, 78 3C/carbo and 79 6C/carbo. Patients receiving carboplatin had poor performance status (ECOG ≥ 1 in 17% cis vs 35% carbo). Table 1 showed similar efficacy outcomes with potentially marginally superior OS with cisplatin. The comparison of efficacy and QOL endpoints for 3 vs 6 cycles of carboplatin showed many similarities. Six cycles of cisplatin-based chemotherapy was associated with a major drop in QOL compared to 3 cycles without showing any clear benefits in efficacy endpoints. **Conclusions:** The QoL benefits of shorter chemotherapy appear to be more marked in patients receiving cisplatin than carboplatin. The efficacy results for 3 cycles of cisplatin were impressive. This study was not powered for non-inferiority. Clinical trial information: NCT06892860. Research Sponsor: Merck; 10.13039/100009945.

Outcomes by treatment arm.

	3C/cis (n=56)	3C/carbo (n=77)	6C/cis (n=54)	6C/carbo (n=80)
CR (%)	16%	10%	14%	12%
PFS (months), median (95% CI)	8.8 (6.5-12.8)	8.0 (5.8-12.0)	8.7 (6.4-18.9)	9.0 (6.6-13.1)
OS (months), median (95% CI)	Not reached (12.8-)	18.5 (12.6-)	21.9 (10.5-)	15.0 (9.8-)
G3 and above TRAE (n)	32	40	49	79
PRO (change from baseline to C7D1)	2.96	-2.51	-13.44	-4.86

Risk and patterns of recurrence for patients (pts) with advanced urothelial carcinoma (aUC) metastatic to liver after response to enfortumab vedotin + pembrolizumab (EVP).

Rishi Raju Patel, Cindy Y. Jiang, Zachariah Thomas, Tanya Jindal, Albert Jang, Jeffrey Yinhong Zhong, Dimitra Bakaloudi, Eugene Oh, Charles B. Nguyen, Salvador Jamie Casas, Abhishek Tripathi, Petros Grivas, Irene Tsung, Matthew T. Campbell, Omar Alhalabi, Ali Raza Khaki, Zhengyi Chen, Pingfu Fu, Vadim S. Koshkin, Jason Robert Brown; University Hospitals Cleveland Medical Center, Cleveland, OH; The University of Texas MD Anderson Cancer Center, Houston, TX; School of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH; Division of Medical Oncology, Department of Oncology, Mayo Clinic Rochester, Rochester, MN; Case Western/University Hospitals, Cleveland; Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; University of Michigan Medical School, Ann Arbor, MI; Rogel Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI; City of Hope Comprehensive Cancer Center, Duarte, CA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; Division of Oncology, Stanford University, Stanford, CA; Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH; Helen Diller Family Comprehensive Cancer Center, Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA; Division of Solid Tumor Oncology, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH

Background: EVP is the preferred frontline regimen in pts with aUC. Despite initial response to treatment, many pts treated with EVP ultimately have progression. We hypothesized that recurrence patterns would differ between pts with and without baseline liver metastases.

Methods: UNITE is a multi-institutional retrospective database capturing clinical and treatment characteristics of pts with aUC receiving systemic therapies. We queried this database to identify pts who achieved an observed response (OR) to EVP. Pts were grouped by initial metastatic sites using a non-mutually exclusive approach. Descriptive statistics were used to summarize observed response rates (ORR) and recurrence patterns at time of progression. Progression-free survival (PFS) from start of EVP was estimated using the Kaplan-Meier method. The effect of liver metastases on PFS was assessed via multivariable Cox regression. Median-follow up time was estimated using the reverse Kaplan-Meier method. Statistical analyses were conducted in RStudio. **Results:** We identified 464 pts treated with EVP (median age 72; 74% male, 80% White). Best ORR in pts with baseline liver metastases (n=77) were complete response 9%, partial response 35%, stable disease 18%, and progressive disease 21%, compared with 18%, 37%, 27%, and 18%, respectively, in pts without baseline liver metastases (n=325). The estimated median follow-up time was 52 weeks (95% CI 48–62). Among pts with initial OR to EVP, those with baseline liver metastases showed a non-significant trend toward shorter PFS (HR 1.35; 95% CI 0.67–2.75; p=0.40) versus those without baseline liver metastases. Among pts with initial OR to EVP and subsequent progression the distribution of sites of recurrences at progression for those with (n = 10) and without (n = 40) baseline liver metastases were: liver (50% vs. 10%), lymph nodes (60% vs. 55%), lungs (50% vs. 38%), bone (20% vs 20%), and primary tumor (20% vs 25%). EVP responders with baseline liver metastases had a numerically higher rate of site-specific metastasis resolution at progression versus those with lymph node or lung metastases (Table). **Conclusions:** Our analysis suggests that liver metastases may be associated with shorter PFS among EVP responders, though these pts frequently do not retain liver metastases at time of progression. Study limitations include retrospective analysis, investigator-assessed response, small sample size, selection and confounding biases. Patterns of recurrence following EVP merits further evaluation. Research Sponsor: None.

Metastatic Site	Pts with Site-Specific Baseline Metastases (n)	Pts with Resolution of Site-Specific Metastases at Progression, n (%)	Pts without Baseline Metastases at Site (n)	Pts who Remained Free of Site-Specific Metastases at Progression, n (%)
Liver	10	5 (50%)	40	36 (90%)
Lymph Nodes	37	12 (32%)	13	10 (77%)
Lungs	26	8 (31%)	24	22 (92%)

Long-term survival update of TRUCE-01: A phase 2 study of preoperative tislelizumab combined with low-dose nab-paclitaxel for muscle-invasive bladder cancer (MIBC).

Zhouliang Wu, Yunkai Qie, Chong Shen, Ning Kang, Peng Li, Kaixuan Du, Hailong Hu; The Second Hospital of Tianjin Medical University, Tianjin, China

Background: The TRUCE-01 study (NCT04730219) previously met its primary endpoint, demonstrating that preoperative tislelizumab combined with low-dose nab-paclitaxel achieved a high clinical complete response (cCR) rate of 52% and a favorable safety profile in patients with muscle-invasive bladder cancer (MIBC). Here, we report the long-term survival outcomes after 4 years of study follow-up. **Methods:** Eligible patients with cT2-4aN0M0 MIBC received three cycles of tislelizumab (200 mg, day 1) plus low-dose nab-paclitaxel (200 mg, day 2) every 3 weeks, followed by radical cystectomy (RC) or maximal transurethral resection of bladder tumor (mTURBT) based on response assessment. The primary endpoint was cCR. Secondary endpoints included event-free survival (EFS), overall survival (OS), disease-specific survival (DSS), and metastasis-free survival (MFS). **Results:** At the clinical data cutoff of October 2025, the median follow-up was 47.4 months (IQR 24.8–53.3). Among the intention-to-treat population ($n = 62$), 25 patients experienced clinical events, including 15 recurrences and 20 deaths (13 due to disease progression, 7 due to non-disease-related causes). Notably, among the 24 patients who elected for bladder preservation, a bladder preservation rate of 75% was achieved (4 due to recurrence requiring salvage radical cystectomy, 2 due to disease progression). The 4-year EFS and OS rates were 59.7% and 67.8%, respectively. Survival analysis stratified by response showed that patients achieving a cCR had significantly superior long-term outcomes compared to non-cCR patients. The cCR group demonstrated a robust and significant benefit in OS (HR 0.28, 95% CI 0.09–0.83, $p = 0.0212$), DSS (HR 0.10, 95% CI 0.02–0.46, $p = 0.0029$), and MFS (HR 0.19, 95% CI 0.06–0.63, $p = 0.0068$). No new safety signals or late-onset immune-related adverse events were observed with extended follow-up. **Conclusions:** With approximately 4 years of median follow-up, preoperative tislelizumab combined with low-dose nab-paclitaxel continues to demonstrate robust and durable survival benefits for patients with MIBC. Clinical trial information: NCT04730219. Research Sponsor: Tianjin Municipal Health Industry; TJWJ2022XK014; Tianjin Municipal Education Commission; 2022ZD069; The Second Hospital of Tianjin Medical University; 2023LC03; Tianjin Institute of Urology; MYSRC202310; The Second Hospital of Tianjin Medical University; 2023LC03; The Second Hospital of Tianjin Medical University; 2022ydey15; The Second Hospital of Tianjin Medical University; 2023LC03; Department of Urology, The Second Hospital of Tianjin Medical University; MNRRRC202313; The Second Hospital of Tianjin Medical University; 2022ydey15; The Second Hospital of Tianjin Medical University; 2022ydey15; Department of Urology, The Second Hospital of Tianjin Medical University; MNRRRC202313; Department of Urology, The Second Hospital of Tianjin Medical University; MNRRRC202313.

Paired Nectin4 expression analysis pre and post enfortumab vedotin and pembrolizumab in urothelial carcinoma.

Michal Sternschuss, Karissa Whiting, Cansu Yol, Merve Basar, Eric Huttenlocher Bent, Aditi Gupta, Ashley M. Regazzi, Firas Ahmed, Oguz Akin, Volkan Beylergil, Scot Anthony Niglio, Daniel E. Lage, Samuel A. Funt, Gopa Iyer, Irina Ostrovskaya, Yanming Zhang, Hikmat Al-Ahmadie, Jonathan E. Rosenberg, David H. Aggen; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering, New York, NY; Genitourinary Oncology, Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY

Background: Enfortumab vedotin and pembrolizumab (EVP) transformed the treatment of urothelial carcinoma (UC), yet resistance remains a challenge. Mechanisms of resistance including changes in target expression are poorly defined. **Methods:** We analyzed an institutional retrospective cohort of patients (pts) who had paired tissue samples obtained pre- and post-EVP. Membranous (mNectin4) and cytoplasmic (cNectin4) expression were measured by immunohistochemistry (H-score). mNectin4 was categorized as negative (<15), weak (15-99), moderate (100-199) or strong (200-300). Changes in Nectin4 were assessed as absolute differences (post-pre) and as scaled log change (%) [$100 \times \log((\text{post} + c)/(\text{pre} + c))$] to capture relative expression changes. Nectin4 dynamics were compared between primary (resistant disease ≤ 6 months from EVP initiation) and acquired resistance (> 6 months) using Wilcoxon rank-sum and fisher's exact tests. **Results:** Of 46 pts with paired samples, 40 had evaluable Nectin4 IHC. Median age was 72, 70% were men, and 30% had upper tract primary. Median H-scores were similar pre- and post-EVP for both mNectin4 (195 [IQR 115, 260] vs 200 [IQR 85, 230]; $p=0.5$) and cNectin4 (0 [IQR 0, 40] vs 0 [IQR 0, 60]; $p>0.9$). Post-EVP mNectin4 was moderate/strong in 29 pts (73%). Complete loss of mNectin4 was uncommon: of five pts (13%) with negative mNectin4 post-EVP, two were negative at baseline and three had weak expression pre-EVP. Post-EVP samples obtained on EV (≤ 21 d from last dose; $n=21$) vs off EV (> 21 d; $n=19$) showed similar changes from pre-EVP for mNectin4 ($p=0.3$) and cNectin4 ($p=0.4$). Nectin4 changes differed by resistance pattern, with primary resistance ($n = 14$) showing a greater relative decrease in mNectin4 expression (median log change -57 vs 3 ; $p = 0.035$) and a relative increase in cNectin4 expression (median log change 52 vs 0 ; $p = 0.029$) compared with acquired resistance ($n = 21$). Paired analyses of *NECTIN4* copy number by FISH will be reported. **Conclusions:** In a paired analysis, most tumors retained substantial mNectin4 expression post-EVP and complete loss was rare, supporting the rationale for Nectin4-targeted strategies in the post-EVP setting. Distinct Nectin4 dynamics suggest greater relevance of target expression changes in primary vs acquired resistance; further studies are needed. Research Sponsor: National Cancer Institute; P30 CA008748; U.S. National Institutes of Health; P50 CA221745.

	All* N=40	Primary resistance N=14	Acquired resistance N=21	p
mNectin4				
Trend				0.11
Decrease	21 (53%)	10 (71%)	10 (48%)	
Increase	17 (43%)	3 (21%)	11 (52%)	
Stable	2 (5.0%)	1 (7.1%)	0 (0%)	
Absolute change, median [IQR]	-13 [-60, 45]	-48 [-100, 0]	10 [-50, 55]	0.2
Log change, median [IQR]	-8 [-57, 23]	-57 [-195, 0]	3 [-21, 21]	0.035
cNectin4				
Trend				0.2
Decrease	12 (30%)	3 (21%)	8 (38%)	
Increase	14 (35%)	8 (57%)	5 (24%)	
Stable	14 (35%)	3 (21%)	8 (38%)	
Absolute change, median [IQR]	0 [-28, 25]	13 [0, 100]	0 [-30, 0]	0.055
Log change, median [IQR]	0 [-137, 67]	52 [0, 304]	0 [-256, 0]	0.029

*Including 5 pts not meeting resistance definitions.

Clinical outcomes for patients (pts) with synchronous versus metachronous metastatic urothelial cancer (mUC) treated with enfortumab vedotin and pembrolizumab (EV-P).

Libin Yan, Lin Lin, Wadih Issa, Shahed Abdullah, Panayiotis Dimitrios Kontoyiannis, Mia Hofstad, Charles Jiang, Qian Qin, Suzanne Cole, Waddah Arafat, Jue Wang, Kevin Dale Courtney, Joseph Vento, Kris Gaston, Vitaly Margulis, Solomon L. Woldu, Yair Lotan, Neil Desai, Andrew Zhuang Wang, Tian Zhang; Division of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Department of Urology, UT Southwestern, Dallas, TX; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Department of Internal Medicine, Division of Hematology/Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX; Division of Hematology and Oncology, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX; Dignity Health Cancer Institute St. Joseph's Hospital and Medical Center, Phoenix, AZ; Vanderbilt University Medical Center, Nashville, TN; Department of Urology, UT Southwestern Medical Center, Dallas, TX; UT Southwestern Medical Center, Dallas, TX; Department of Radiation Oncology, UT Southwestern Medical Center, Dallas, TX; Department of Internal Medicine, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX

Background: Synchronous versus metachronous metastases in mUC has prognostic significance, and EV-P has emerged as standard first-line therapy for pts with mUC. How primary disease in synchronous mUC should be best treated remains unclear. This study evaluated clinical outcomes of pts with synchronous vs metachronous mUC treated with EV-P. **Methods:** A retrospective analysis of all consecutive pts with mUC treated EV-P at UTSW was performed. Patients were grouped by synchronous mUC or metachronous mUC. Baseline characteristics were compared using Wilcoxon rank-sum and Chi-squared tests. Overall survival (OS) and progression-free survival (PFS) were analyzed using Cox proportional hazards models. **Results:** For 159 pts with mUC treated with EV-P between 9/2020 and 12/2025, 40 had synchronous mUC and 119 had metachronous mUC. Baseline characteristics were similar with median age 71.5 years vs 73.0 years ($p=0.90$), male 75% vs 94% ($p=0.76$), and visceral metastases (20% vs 26%, $p=0.58$). In metachronous mUC, 76 (63.9%) had prior cystectomy and 42 (35.3%) had prior radiation as definitive treatment. Patients with metachronous mUC demonstrated a median PFS of 16.0 months vs not reached (NR) for patients with synchronous mUC (HR 1.95, 95% CI 1.05–3.62; $p = 0.035$). Similarly, the median OS was 21.9 months for metachronous mUC vs not reached in the synchronous mUC (HR 2.61, 95% CI 1.24–5.49; $p = 0.011$). Median cycles of EV-P was 13.5 for synchronous mUC vs 10 for metachronous mUC. For synchronous mUC, 22 (55.0%) underwent cystectomy and 8 (20.0%) underwent radiation as consolidative treatment. **Conclusions:** Synchronous and metachronous mUC treated with EV-P have significantly different disease courses on EV-P. Metachronous mUC has earlier progression on EV-P, needing more treatment options in refractory disease. Consolidation treatment for synchronous mUC needs further prospective trials for optimal outcomes. Research Sponsor: None.

Comprehensive baseline characteristics and clinical outcomes.			
Characteristic	Synchronous met	Metachronous met	P value
Number of patients	40	119	
Age at treatment initiation, median (IQR)	71.5 (64.5–76.0)	73.0 (64.0–78.0)	0.904
Male sex, n (%)	30 (75.0%)	94 (79.0%)	0.759
Prior local therapy			
Prior radical cystectomy	N/A	76 (63.9%)	
Prior radiation therapy	N/A	42 (35.3%)	
Metastatic burden			
Any visceral metastasis	8 (20.0%)	31 (26.1%)	0.578
Liver metastasis	6 (15.0%)	17 (14.3%)	1.000
Treatment and outcomes			
EV-P cycles, median (range)	13.5 (1–39)	10.0 (1–57)	0.281

Use of *NECTIN4* expression inferred from circulating chromatin to predict response and survival to enfortumab vedotin (EV) in metastatic urothelial carcinoma.

Rashad Nawfal, Gunsagar Singh Gulati, Damien Vasseur, Shahabeddin Sotudian, Karl Semaan, Ji-Heui Seo, Noa Phillips, John Canniff, Hunter Savignano, Rachel Trowbridge, Ilana Bensussen Epstein, Gabriella Rickards, Razane El Hajj Chehade, Ze Zhang, Gwo-Shu Mary Lee, Joaquim Bellmunt, Sylvan C. Baca, Matthew L. Freedman, Toni K. Choueiri; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA

Background: APEX (Associating Plasma Epigenomics with eXpression) is a machine-learning framework that infers genome-wide gene expression in cancer from plasma cell-free chromatin Immunoprecipitation sequencing (cfChIP) by integrating signal from multiple histone marks and fragmentomic features, enabling enhanced transcriptional readouts from liquid biopsy without tissue sampling. We investigated whether APEX can noninvasively quantify *NECTIN4* expression to predict outcomes with EV, a *NECTIN4*-targeted antibody-drug conjugate, in metastatic bladder cancer. **Methods:** Baseline plasma (1 mL) was collected from patients with metastatic bladder cancer within 90 before to 8 days after start of EV monotherapy and profiled by cfChIP-seq, followed by APEX-based tumor gene-expression inference. APEX-inferred *NECTIN4* expression was dichotomized into high and low groups by the cohort median and tested for association with objective response (CR/PR vs SD/PD). Progression-free survival (PFS) and overall survival (OS) were analyzed using log-rank test and multivariable Cox regression model, accounting for the presence of bone or liver metastases and cfDNA tumor fraction. APEX performance was then compared against *NECTIN4* locus signal from individual histone marks, plasma tumor fraction, and *NECTIN4* copy-number status/amplification. **Results:** In the EV-treated cohort ($n=24$), baseline APEX-inferred *NECTIN4* expression was significantly higher in responders versus non-responders ($p = 0.002$) and outperformed *NECTIN4* estimates derived from single histone-mark features, tumor fraction, and *NECTIN4* copy number. Patients with high plasma-inferred *NECTIN4* had an objective response rate of 58%, whereas no responses were observed among those with low inferred *NECTIN4*, supporting strong negative predictive value. High baseline APEX-inferred *NECTIN4* was also significantly associated with improved progression-free and overall survival (HR = 0.22, 95%CI: 0.08 – 0.65, $p = 0.005$ and HR = 0.27, 95%CI: 0.10 – 0.75, $p = 0.008$, respectively), with stronger associations than plasma tumor fraction, *NECTIN4* copy number/amplification, or individual histone-mark coverage. In multivariable Cox models, APEX-inferred *NECTIN4* remained independently associated with survival. Moreover, responders were enriched for urothelial luminal genes known to associate with *NECTIN4* expression and favorable outcomes, while non-responders showed increased activation of epithelial-mesenchymal transition-related genes, known to associated with worse outcomes. **Conclusions:** A machine learning framework for plasma-based inference of tumor gene expression identifies plasma-based *NECTIN4* as a clinically actionable, expression-based biomarker that predicts EV response and survival in metastatic bladder cancer. Research Sponsor: None.

Cost-effectiveness analysis of first-line (1L) therapies for advanced urothelial carcinoma (aUC) from a U.S. payer perspective.

Prateek Jain, Prithvi Raghavan, Harshit Narula, Syed Arsalan Ahmed Naqvi, Irbaz Bin Riaz, Parminder Singh; Sinai Hospital Baltimore, Baltimore, MD; Sinai Hospital of Baltimore, Baltimore, MD; Sinai Hospital of Baltimore, Baltimore, MD; Mayo Clinic Arizona, Phoenix, AZ; Division of Hematology and Medical Oncology, Mayo Clinic Arizona, Phoenix, AZ

Background: Recent years have seen a shift in aUC management following approval of enfortumab vedotin–pembrolizumab (EV-P) and gemcitabine/cisplatin plus nivolumab (GC-NIVO) as first-line therapies. Despite improved clinical outcomes, their relative economic value remains uncertain. Herein, we conducted a cost-effectiveness analysis of current 1L regimens in aUC from a U.S. payer perspective using 2026 pricing. **Methods:** A partitioned survival model with three health states (progression-free [PF], progressed disease [PD], and death) was developed over a 10-year horizon from a U.S. payer perspective. Analyses focused on cisplatin-eligible patients. Survival data were reconstructed from published Kaplan–Meier curves and extrapolated using parametric survival models. Treatment dosing, schedules, and duration were modeled according to trial protocols. Patients receiving gemcitabine/cisplatin without progression were modeled to receive avelumab maintenance (GC→AVEL). Subsequent-line therapy costs were applied at incident progression, and grade ≥ 3 adverse event costs and disutilities were applied as one-time events. Drug acquisition costs (2026 USD) were based on average sales prices from the Centers for Medicare & Medicaid Services. Costs and quality-adjusted life years (QALYs) were discounted at 3% annually. Incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB) were evaluated at willingness-to-pay (WTP) thresholds of \$100,000, \$150,000, and \$200,000 per QALY. Parameter uncertainty was characterized using probabilistic sensitivity analysis. **Results:** In the base-case analysis, total discounted costs and QALYs were \$90,269 and 1.62 for GC→AVEL, \$131,836 and 2.09 for GC-NIVO, and \$1,451,885 and 2.77 for EV-P. Compared with GC→AVEL, GC-NIVO gained 0.46 QALYs at an incremental cost of \$41,567, resulting in an ICER of \$89,501 per QALY and positive NMB across all evaluated WTP thresholds. Compared with GC→AVEL, EV-P gained 1.15 QALYs at an incremental cost of \$1.36 million (ICER \$1.19 million per QALY). Compared with GC-NIVO, EV-P gained 0.68 QALYs at an incremental cost of \$1.32 million (ICER \$1.93 million per QALY), exceeding all evaluated WTP thresholds. In a scenario analysis limiting EV-P to 10 treatment cycles, total costs decreased to \$287,360, with ICERs of \$172,000/QALY versus GC→AVEL and \$225,000/QALY versus GC-NIVO, remaining above the \$150,000/QALY threshold. **Conclusions:** Using updated 2026 pricing, GC-NIVO is likely to be the most cost-effective first-line regimen for cisplatin-eligible patients with aUC. EV-P offers the greatest clinical benefit but is not cost-effective at current prices. A major limitation of this study is cross-trial variability in study populations and design, limiting the validity of head-to-head economic comparisons. Research Sponsor: None.

A novel oncolytic vaccinia virus armed with IL-21 and 4-1BBL for intravesical treatment of NMIBC: Preclinical efficacy and first-in-human safety evaluation.

Shun Zhang, Hailong Liu, Ding Xu, Xiuwu Pan, Ying Wang, Xingang Cui, Haibo Shen; Department of Urology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Urology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; Shanghai Institute of Immunology, Shanghai, China

Background: Oncolytic viruses are emerging cancer immunotherapies. For non-muscle-invasive bladder cancer (NMIBC), intravesical delivery allows high local exposure with limited systemic toxicity. This study was conducted to evaluate anti-tumor efficacy, mechanism and safety of KM1, a novel developed oncolytic vaccinia virus modified with tyrosine kinase deletion, L025 and A46R gene deletion, and armed with interleukin 21 and 4-1BBL in murine models and human. **Methods:** In vitro assays assessed virus replication, cytotoxicity, and transgene expression in human and murine bladder cancer cell lines and organoids. In vivo studies assessed immune activation, toxicity, and antitumor efficacy in murine subcutaneous and orthotopic bladder tumor models. An investigator-initiated phase 1a trial enrolled NMIBC patients who had failed prior BCG therapy or declined further BCG. This multicenter, single-arm study used 3+3 dose-escalation with primary endpoints of safety and tolerability (AE and DLTs). Planned dose levels were 2×10^9 PFU (DL1), 5×10^9 PFU (DL2), and 1×10^{10} PFU (DL3) per instillation. Following completion of DL1 and DL2, the protocol was amended to discontinue further dose escalation (DL3 was not opened) and to enroll an expansion cohort at DL1 (additional n=3) to further characterize safety/tolerability and PK/PD at the putative recommended dose. The induction regimen consisted of bladder irrigation with sucrose monolaurate, followed by intravesical KM1 retained for 2 hours, given twice weekly for 3 weeks and then once weekly for 3 weeks. Subsequent maintenance therapy comprised three intravesical KM1 instillations every 3 months. **Results:** KM1 selectively replicated in human and murine bladder cancer cells, induced high IL-21 and 4-1BBL secretion. Supernatant from KM1-infected cells activated CD8⁺ T cells and enhanced tumor-killing *in vitro*. *In vivo*, KM1 showed better antitumor efficacy than BCG, increased CD8⁺ T and NK cell infiltration and function. Depletion of either population diminished efficacy. In the phase 1a study, 12 patients received intravesical KM1 (DL1, n=9 [including n=3 expansion]; DL2, n=3) and were evaluable. Ten TEAEs were reported, predominantly grade 1–2; the most common were noninfective cystitis (5/12, 41.7%) and urinary tract pain (4/12, 33.3%). One DL1 patient experienced a DLT of transient, likely treatment-related grade 3 liver injury that resolved within 1 week without sequelae. No KM1 DNA was detected in saliva, blood, or feces at any assessed time point. At a median follow-up of 10.1 months, all patients remained recurrence-free by 6 months (CR 12/12; 100%). **Conclusions:** KM1 showed selective replication, oncolysis, and immune activation in preclinical models. Early clinical data suggest favorable safety and promising antitumor activity of intravesical KM1 in NMIBC. Clinical trial information: ChiCTR2400086709. Research Sponsor: Shenzhen Huayao Kangming Biopharmaceutical Co., Ltd.

Keratin 19 (KRT19) as a circulating biomarker to measure disease burden and guide treatment in urothelial cancer.

Eric James Miller, Shu-Hsiang Wang, Marcio A. Diniz, Sudeh Izadmehr, Jonathan F. Anker, John Sfakianos, Reza Mehrazin, Matthew I. Milowsky, Sumanta Kumar Pal, Kai Nie, Seunghee Kim-Schulze, Matthew D. Galsky; Mount Sinai Tisch Cancer Center, New York, NY; Icahn School of Medicine at Mount Sinai Tisch Cancer Institute, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY; UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC; City of Hope Comprehensive Cancer Center, Duarte, CA; Department of Immunology and Immunotherapy, Icahn School of Medicine at Mount Sinai, New York, NY; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY

Background: Circulating tumor DNA (ctDNA) has emerged as a valuable biomarker in urothelial cancer but remains limited by cost and turnaround time. Keratin 19 (KRT19) is a cytoskeletal protein that is highly and specifically expressed in urothelial tumor tissue in The Cancer Genome Atlas (TCGA) urothelial cancer cohort. Based on this tumor specific expression, we hypothesized that circulating KRT19 levels could serve as a rapid, inexpensive measure of disease burden to guide systemic therapy for urothelial cancer. **Methods:** Two patient cohorts from completed clinical trials were analyzed. HCRN GU16-257, a phase 2 trial of gemcitabine, cisplatin, and nivolumab as organ-sparing treatment for localized muscle-invasive bladder cancer, included 76 patients evaluable for KRT19 with median follow-up of 30 months. HCRN GU14-182, a phase 2 switch maintenance trial of pembrolizumab versus placebo following first-line chemotherapy for metastatic urothelial cancer, included 46 patients evaluable for KRT19 in the pembrolizumab arm with median follow-up of 12.9 months. Serum KRT19 levels were quantified using Olink proteomics technology alongside 91 additional proteins. Cox proportional hazards models assessed associations between KRT19 expression and clinical outcomes, with adjustment for multiple comparisons using false discovery rate correction. **Results:** In the GU16-257 cohort, among 92 peripheral blood analytes tested at baseline (C1D1), KRT19 demonstrated the strongest association with overall survival. Elevated baseline KRT19 was independently associated with inferior overall survival (HR 2.62, adjusted $p=0.016$) and metastasis-free survival (HR 3.01, adjusted $p=0.001$). A decrease in KRT19 from C1D1 to C3D1 was associated with improved overall survival (HR 0.59, unadjusted $p=0.024$) and metastasis-free survival (HR 0.60, unadjusted $p=0.041$). In GU14-182, elevated baseline KRT19 was associated with inferior overall survival (HR 2.11, adjusted $p=0.034$) and progression-free survival (HR 1.57, unadjusted $p=0.024$). Optimal KRT19 cutpoints enabled significant risk stratification for mortality and disease progression in both cohorts. Analysis of an independent peripheral blood single-cell RNA sequencing cohort from patients with urothelial cancer confirmed epithelial cells as the predominant source of circulating KRT19. **Conclusions:** KRT19 represents a promising, readily measurable serum biomarker with specificity for urothelial cancer. Both baseline levels and on-treatment changes correlate with disease progression and survival. Further validation of KRT19 as a tool to assess disease burden and guide treatment decisions in urothelial cancer is warranted. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Preliminary results of a single-arm, multi-center, prospective clinical study of disitamab vedotin combined with toripalimab and pelvic lymph node dissection for bladder preservation in patients with cT2-4aN0M0 bladder urothelial carcinoma and HER2 expression $\geq 2+$ after maximal TURBT.

Tianhang Lan, Wenlong Zhong, Qihong Tan, Dongxi Zhu, Shengming Ran, Mingchao Gao, Wenjie Li, Junyi Xie, Tianxin Lin, Jian Huang, Wang He; The Second Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China; The Second Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: With the evolution of different treatment eras, the clinical complete response (cCR) rate of bladder cancer has been progressively increasing, while the lymph node metastasis rate has still not improved significantly. Particularly, patients with HER2 overexpression are at a higher risk of lymph node metastasis, which poses a major challenge to bladder-sparing therapy for patients with muscle-invasive bladder cancer (MIBC). This study aims to establish a novel bladder-preserving treatment model by combining local therapy enhanced with pelvic lymph node dissection (PLND) and systemic therapy with Disitamab Vedotin and Toripalimab. **Methods:** Patients with cT2-4aN0M0 MIBC and HER2 expression $\geq 2+$ were enrolled. The primary endpoint was 2-year bladder-intact disease-free survival rate. After maximal transurethral resection of bladder tumor (TURBT), patients received Toripalimab (3mg/kg, Q2W) combined with Disitamab Vedotin (2mg/kg, Q2W) for 6 cycles, followed by TURBT and PLND. Those with cCR or partial response (PR) continued the combined therapy for another 6 cycles. Patients achieving cCR after 12 cycles of combined therapy received maintenance Toripalimab (240mg, Q3W) for 1 year. Non-cCR patients received comprehensive treatment or salvage radical cystectomy (RC). **Results:** As of December 2025, 21 patients were enrolled, with a median age of 66 years (range: 37–82). The primary endpoint was not yet reached. Efficacy assessment was performed in 14 patients at Week 12: 10/12 (85.8%) achieved cCR, while 1 patient had stable disease (SD) and 1 had progressive disease (PD). Among 10 patients who underwent TURBT and PLND, pathological complete response (pT0N0M0) was achieved in 90.0%, and 1 patient was postoperatively staged as pT0N1M0. Patients with SD or PD underwent RC. All patients experienced treatment-related adverse events (TRAEs) of any grade. The most common TRAEs were pruritus (75.00%), paresthesia (68.75%), and elevated ALT (43.75%), all of which were Grade 1–2. One patient developed a Grade 3 adverse event (AE), which was severe urinary tract infection. No TRAEs of Grade ≥ 4 were observed. **Conclusions:** The novel bladder-sparing modality of Disitamab Vedotin combined with Toripalimab plus PLND after maximal TURBT currently demonstrates favorable efficacy and safety. Long-term outcomes warrant further investigation. Clinical trial information: ChiCTR2400081555. Research Sponsor: Rongchang Biopharmaceutical (Yantai) Co., Ltd; Shanghai Junshi Biosciences Co., Ltd; National Natural Science Foundation of China; Wang He; the National Key Research and Development Program of China; Wang He.

Urinary tumor DNA–guided de-escalation of systemic immunotherapy in extensive very high risk non–muscle-invasive bladder cancer.

Yunkai Qie, Zihan Xue, Jiazeng Zhao, Shan Liang, Liliang Li, Guoqiang Han, Zhouliang Wu, Chong Shen, Qian Ziliang Sr., Hailong Hu; The Second Hospital of Tianjin Medical University, Tianjin, China; Daqing Oilfield General Hospital, Daqing, China; Hongyuan Biotech, Suzhou, China

Background: Non-muscle-invasive bladder cancer (NMIBC) has entered the era of systemic immunotherapy. Large randomized trials, including CREST, POTOMAC, and ALBAN, have explored long-term systemic immunotherapy in NMIBC, yet the clinical benefit remains heterogeneous and is often accompanied by substantial toxicity. Urinary tumor DNA (utDNA) has emerged as a promising biomarker for molecular response assessment, yet its role in guiding treatment de-escalation has not been established. We evaluated whether utDNA negativity after complete response (CR) could support safe early treatment cessation of systemic therapy in patients with extensive very-high-risk NMIBC (VHR-NMIBC). **Methods:** Patients with extensive VHR-NMIBC who achieved CR after initial systemic therapy with the PD-1 inhibitor tislelizumab plus low-dose paclitaxel were included from a prospective cohort. After CR assessment, some patients underwent low-coverage utDNA testing as part of routine clinical decision-making following clinician–patient discussion. Patients with negative utDNA completed three additional cycles and subsequently stopped systemic therapy (utDNA-guided de-escalation group), whereas those who continued treatment beyond this point were categorized as the longer treatment-exposure group. Efficacy and safety outcomes included survival endpoints and adverse events (AEs) with exposure-adjusted incidence rates. **Results:** With a median follow-up of 42.8 months, 54 patients achieving CR were evaluable. Among them, 21 with negative utDNA status completed three additional cycles and underwent planned treatment cessation, while 33 continued systemic therapy with longer treatment exposure. Across key efficacy endpoints, outcomes were comparable between the utDNA-guided de-escalation and longer treatment-exposure groups, with no significant differences in recurrence-free survival (RFS; HR 1.37, 95% CI 0.21–8.87, $P = 0.73$), overall survival (OS; HR 2.48, 95% CI 0.12–53.7, $P = 0.51$), or duration of response (DOR; HR 1.33, 95% CI 0.21–8.50, $P = 0.76$). A difference in radical-cystectomy-free survival was observed (short vs long: HR 4.97, 95% CI 1.03–23.9, $P = 0.03$). Long-course treatment was associated with a higher cumulative incidence of any-grade AEs (88.1% vs 72.5%) and more AE types (median 5 vs 2, $P < 0.001$). Exposure-adjusted AE rates per cycle were lower in the long-course group (IRR 0.50, 95% CI 0.42–0.60, $P < 0.001$), while grade ≥ 3 AEs occurred in 2.9% and 9.5% of patients in the short- and long-course groups, respectively, predominantly during later treatment phases. **Conclusions:** UtDNA negativity after complete response may provide a molecular basis for individualized treatment duration, highlighting the potential role of liquid biopsy in guiding precision treatment tailoring and warranting prospective validation in larger biomarker-driven studies. Clinical trial information: NCT04730232. Research Sponsor: None.

Evidence implicating human papillomavirus in bladder carcinogenesis: A case-control study.

Xueying Zhang; Jilin Cancer Hospital, Changchun, Jilin, China

Background: The etiology of high-risk oncogenic human papillomavirus (HPV) subtypes with signature cytomorphological changes such as koilocytosis in bladder cancer (BCa) carcinogenesis still remains controversial and insufficiently investigated. We evaluated the diagnostic concordance rate between HPV-DNA test with urine HPV related cytomorphological findings in BCa urine samples. **Methods:** A retrospective case-control study was conducted. A total of 172 HPV-positive urine cytology specimens from patients with primary BCa treated at our hospital between January 2020 and December 2024 were included as the study group. During the same period, of 172 HPV-negative urine cytology specimens from primary BCa were selected as the control group. HPV DNA was detected by in situ hybridization was utilized. Immunohistochemistry (IHC) was performed to assess p16^{INK4a} protein expression as a surrogate marker of functional HPV activity. Cytomorphologic changes that had concurrent liquid-base cytology were identified using The Paris System for Reporting Urinary Cytology (TPS) criteria. Statistical analyses were performed using chi-square tests and fisher's exact tests. **Results:** Overexpression of p16^{INK4a} was observed in 82.2% (140/172) of the HPV-positive group and showed a high level of concordance with HPV infection status (Kappa=0.812, $p<0.001$). Among the HPV-positive group, high-risk HPV types accounted for 88.9% (152/172) with HPV-16 (114/152, 75.6%) and HPV-18 (38/152, 24.4%) being the predominant subtypes. A p16^{INK4a} protein expression from HPV-negative group was detected which was significantly lower than in the positive group (13/172, 7.56%, $p<0.001$). HPV infection cytomorphology was identified, with 48.6% (83/172) koilocytes (52/172, 30.23%) either alone or in addition to basaloid clusters (16/172, 9.3%) and atypical squamous cells (ASCs) (15/172, 8.72%) identified using TPS from the HPV-positive group, and a significantly lower rate of 6.1% (10/172, $p<0.001$) was identified from the HPV-negative group. **Conclusions:** HPV plays an etiological role in carcinogenesis and contributes to a worse prognosis for patients with BCa development. The identification of cytomorphologic changes in urine cytology is a significant and underutilized piece of etiological evidence supporting a role for HPV in bladder carcinogenesis. It provides a reliable direct and visible link between the viral cytopathic effect and the urothelial cells. Integrating routine cytological assessment with modern molecular testing in urine samples could better define its role as an oncogenic driver in specific BCa variants. Recognizing this association has implications for risk stratification, screening in high-risk populations, and potential therapeutic avenues. Research Sponsor: The Science & Technology Committee of Jilin Province, China; JLKJT2024081451JLZLYTY.

Clinical outcomes with *ERBB2* gene amplification and activating mutations in muscle-invasive bladder cancer patients treated with neoadjuvant chemotherapy.

Earle F. Burgess, Landon Carter Brown, Michael Joseph McCormack Jr., Ericson Stoen, Metamia Ciampricotti, Edward Williams, James Thomas Symanowski; Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Charlotte, NC; Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston Salem, NC; Tempus AI, Inc., Chicago, IL; Tempus AI, Chicago, IL

Background: Activating *ERBB2* mutations (mut) are associated with improved pathologic response (pCR) to neoadjuvant chemotherapy (NAC) in patients with muscle-invasive bladder cancer (MIBC). However, the impact of *ERBB2* gene amplification (amp) on pCR and of aggregate *ERBB2* gene variants (amp and mut) on relapse and survival is unknown. We previously reported that high tumor mutational burden (TMB) is associated with improved pCR and relapse-free survival (RFS) in a cohort of MIBC patients treated with cisplatin-based NAC followed by cystectomy (Burgess et al. GU ASCO '26). In the current analysis, we assessed the impact of *ERBB2* gene variants on clinical outcomes in the previously reported cohort. **Methods:** 91 patients with MIBC who received cisplatin-based NAC followed by radical cystectomy underwent genomic analysis of diagnostic transurethral resection of bladder tumor specimens with the Tempus xT platform. Sample size was prespecified by statistical design. Correlation of *ERBB2* gene variants with TMB and clinical outcomes was performed using logistic regression, Cox proportional hazards models, and Kaplan-Meier techniques. **Results:** Median follow for the cohort was 63.6 months. pCR was achieved in 31.9%. Thirty-eight (41.8%) patients relapsed. Only 4 (4.4%) received adjuvant immune checkpoint inhibition (ICI). *ERBB2* mut and amp were exclusively found in 4 (4.4%) and 13 (14.3%) patients, respectively. All *ERBB2* mut were p.S310F. pCR occurred in 3 (75%) patients with mut and 6 (46.2%) patients with amp. In those with amp and no pCR (7), 4 were ypTaNo or ypT1No. In aggregate, the presence of *ERBB2* gene variants (mut + amp, n = 17) was associated with an improved pCR rate compared to no *ERBB2* gene variant (OR = 3.038, p = 0.048). *ERBB2* variants (mut + amp) were not clearly associated with a TMB > 10 Mut/Mb (OR = 2.217, p = 0.178). Five patients with *ERBB2* gene variants relapsed (29.4%, OR = 0.518, p = 0.288). Three (75%) mut and ten (76.9%) amp patients remain alive. The median RFS for patients with and without *ERBB2* gene variants in aggregate is 124.1 and 54.7 months (HR = 0.460, p=0.094). The median overall survival (OS) for patients with and without *ERBB2* gene variants is Not Reached and 107.6 months (HR = 0.381, p=0.098). **Conclusions:** The impact of *ERBB2* gene variants (mut + amp) on survival in MIBC-patients treated with NAC has not been previously reported. In this cohort collected before widespread use of peri-operative ICI, the presence of *ERBB2* gene variants was associated with improved pCR rates and showed strong trends for improved RFS and OS but not clearly associated with high TMB. These findings establish a prognostic role for *ERBB2* amp in addition to previously reported *ERBB2* mut in patients with MIBC. Whether peri-operative use of ICI or *ERBB2*-targeted agents may influence these findings warrants further investigation. Research Sponsor: Atrium Health Foundation.

Impact of FGFR3 pathway activation in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy.

Earle F. Burgess, Landon Carter Brown, Liang Liu, Kirk L. Pappan, Gregory Mayhew, Michael Joseph McCormack Jr., Nury Steuerwald, Ericson Stoen, Edward Williams, Metamia Ciampricotti, Wei Zhang, James Thomas Symanowski; Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Charlotte, NC; Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC; GeneCentric Therapeutics, Durham, NC; Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC; Tempus AI, Chicago, IL; Tempus AI, Inc., Chicago, IL

Background: The prognostic value of FGFR3 pathway activation in patients with muscle-invasive bladder cancer (MIBC) treated with neoadjuvant chemotherapy (NAC) has not been established. Activation of FGFR3 signaling drives a subset of urothelial bladder cancers and classically results from pathogenic gene mutations (mut) or fusions (fus). Additionally, an RNA signature (FGFR-PRS) representing activation of the FGFR3 pathway independent from pathogenic FGFR3 mut or fus has been identified (Eisner et al. Clin Can Res 2024). We previously reported that high tumor mutational burden (TMB) may be associated with improved pathological complete response (pCR) and survival in a cohort of MIBC patients treated with cisplatin-based NAC (Burgess et al. GU ASCO '26). In the current analysis, we assessed the impact of FGFR3 pathway activation detected by either FGFR3 gene mut/fus or FGFR-PRS (+) on clinical outcomes in the previously reported cohort. **Methods:** 91 patients with MIBC who received cisplatin-based NAC followed by radical cystectomy underwent genomic analysis of diagnostic transurethral resection of bladder tumor specimens with the Tempus xT platform. Sample size was prespecified by statistical design. A subset of 61 patients had sufficient RNA for FGFR-PRS analysis. Correlation of FGFR3 molecular status with TMB and clinical outcomes was performed using logistic regression, Cox proportional hazards models, and Kaplan-Meier techniques. **Results:** Median follow up for the cohort was 63.6 months. pCR was achieved in 31.9%. 41.8% of patients relapsed. FGFR3 mut were found in 8 (8.8%) and included p.R248C (n = 2), p.S249C (n = 5), and p.G370C (n = 1). One (1.1%) patient had a FGFR3-TACC3 fus. In the subset with RNA analysis (n = 61), FGFR-PRS (+) was detected in 33 (54.1%), of which 28 (84.8%) were FGFR3 wild type (wt) without detected mut/fus. pCR occurred in 12.5% and 33.7% with and without FGFR3 mut [OR 0.281, p = 0.428]. pCR was similar regardless of FGFR-PRS status [OR 1.372, p = 0.602]. All tumors with FGFR3 mut/fus (n = 9) had TMB < 10 Mut/Mb. Nineteen (57.6%) tumors with FGFR-PRS (+) had TMB < 10 compared to 13 (46.4%) of FGFR-PRS (-) tumors. Six (75%) patients with FGFR3 mut [OR 3.188, p = 0.064] and 10 (30.3%) with FGFR-PRS (+) [OR 1.087, p = 0.999] relapsed. Patients with FGFR3 mut had inferior relapse-free survival (RFS) [HR 2.58, p = 0.028], but those with FGFR-PRS (+) did not [HR 1.37, p = 0.451]. **Conclusions:** The presence of FGFR3 mutations was associated with an inferior relapse rate and RFS in this MIBC cohort treated with cisplatin-based NAC. FGFR3 pathway activation by RNA signature (FGFR-PRS+) was not associated with inferior outcomes. Whether peri-operative FGFR3 inhibition improves prognosis in MIBC patients with FGFR3 mutations should be studied. Research Sponsor: Atrium Health Foundation.

PUNCH03: Preliminary results from 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, Cheng Luo, Yukun Wu, Jiahao Lei, 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. Finally, pts received at least 1 year of tislelizumab (200 mg, Q3W, ivgtt). Meanwhile, pts were administered 3 - 5 cycles of RC48 (2.0 mg/kg, Q2W, ivgtt) and received 18 instillations of BCG. 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 (defined as no reappearance of high grade or T1 tumors or clinical stage development after the therapy). 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. **Results:** By Aug. 2025, 24 eligible pts were enrolled and analyzed (male 87.5%; median age 63 years (38-85); IHC 2+ =58.3%, IHC 3+ =41.7%; tumor size $\geq$ 3 cm (50%); cT1=100.0%; 75.0% multiple papillary tumours. Median follow-up was 6.1 months (3.1-14.2), the median number of tislelizumab cycles was 10 (4-16) and RC48 cycles was 6 (4-8). All pts completed tislelizumab and RC48 treatment during the induction therapy. During the follow-up, only two pts showed reappearance and one pt received radical cystectomy. The bladder-preservation rate was 95.8% (95%CI, 90.7%-100%). The common treatment related adverse events (TRAEs) of any grade were fatigue (54.2%), alopecia (33.0%), anorexia (33.0%) and peripheral neuropathy (16.8%). None 3-5 grade of TRAEs were observed. **Conclusions:** Our preliminary results supported the use of disitamab vedotin combined with tislelizumab and BCG as a bladder-preserving therapy for Her2-positive HR NMIBC pts. Clinical trial information: ChiCTR2400093839. Research Sponsor: None.

Cost-effectiveness analysis in the era of systemic immunotherapy for BCG-naïve high-risk non-muscle-invasive bladder cancer in the United States, the United Kingdom, and China.

Zihan Xue, Yunkai Qie, Xiaohua Li, Shan Liang, Jiazeng Zhao, Liliang Li, Houyuan Chen, Yuda Lin, Guoqiang Han, Chong Shen, Zhouliang Wu, Hailong Hu; The Second Hospital of Tianjin Medical University, Tianjin, China; The Second Hospital of Tianjin Medical University, Tianjin, Tianjin, China; Daqing Oilfield General Hospital, Daqing, China

Background: Non-muscle-invasive bladder cancer (NMIBC) has entered the era of systemic immunotherapy, with randomized trials evaluating the addition of systemic immunotherapy to BCG to improve disease control. The cost-effectiveness of combining immune checkpoint inhibitor (ICI) with BCG in BCG-naïve high-risk NMIBC (HR-NMIBC) remains unclear. We therefore conducted a multinational cost-effectiveness analysis in the United States, United Kingdom, and China based on the CREST and POTOMAC studies. **Methods:** We developed a Markov model to evaluate treatment strategies for patients with BCG-naïve HR-NMIBC over a 5-year time horizon from healthcare payer perspectives, with health outcomes measured in quality-adjusted life-years (QALYs). Total costs, QALYs, and incremental cost-effectiveness ratios (ICERs) were calculated for each strategy. Model robustness was assessed using deterministic and probabilistic sensitivity analyses. **Results:** Health outcomes were comparable across strategies, with BCG, durvalumab plus BCG, and sasanlimab plus BCG yielding 4.11, 4.31, and 4.18 QALYs, respectively. In the US, durvalumab plus BCG increased costs by \$159,021 compared with BCG, resulting in an ICER of \$827,706 per QALY, exceeding the willingness-to-pay (WTP) threshold of \$150,000 per QALY. In the UK, the corresponding ICER was £503,944 per QALY, far above the WTP threshold of £20,000 per QALY. In China, the ICER reached ¥3,860,692 per QALY, exceeding the threshold defined as three times the national per-capita GDP (¥257,145). Sasanlimab plus BCG was strictly dominated by durvalumab plus BCG in all settings. Consequently, neither systemic immunotherapy-based strategy was cost-effective under the evaluated WTP thresholds. BCG was optimal in all probabilistic simulations, and ICI prices were the primary drivers of cost-effectiveness for systemic immunotherapy-based strategies. **Conclusions:** Despite modest clinical benefits, the high cost of systemic immunotherapy plus BCG precludes cost-effectiveness across health care systems, with BCG alone remaining the preferred strategy under current pricing. Future efforts should focus on drug price reductions and precision patient selection to improve the value proposition of early systemic immunotherapy. Research Sponsor: None.

	Costs (\$; US)	Costs (£; UK)	Costs (¥; China)	Incremental costs (\$; US)	Incremental costs (£; UK)	Incremental costs (¥; China)	Effectiveness (QALYs)	ICER (\$/QALY; US)	ICER (£/QALY; UK)	ICER (¥/QALY; China)
BCG	48,828	21,307	119,383	-	-	-	4.11	-	-	-
Durvalumab + BCG	207,849	118,126	861,110	159,021	96,819	741,728	4.31	827,706	503,944	3,860,692
Sasanlimab + BCG*	309,654	138,329	932,331	260,826	117,023	812,948	4.18	3,726,091	1,671,751	1,1613,542

*The Sasanlimab plus BCG strategy is strictly dominated by the Durvalumab plus BCG strategy (higher cost and lower effectiveness).

Final results from a phase II study of tislelizumab combined with radiotherapy as bladder-preserving treatment for high-risk non-muscle-invasive bladder cancer patients unresponsive to Bacillus Calmette-Guerin.

Zhiyong Li, Jingwei Ye, Yang Liu, Kai Yao, Zhiming Wu, Yunlin Ye, Xiangdong Li, Fangjian Zhou, Zikun Ma, Liru He, Zhuowei Liu; Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Radical cystectomy (RC) was the standard of care for high-risk non-muscle-invasive bladder cancer (HR NMIBC) patients with Bacillus Calmette-Guerin (BCG)-unresponsive papillary tumors. Clinical unmet need was to explore non-surgical treatment options for patients who were ineligible for or declined RC. Our study was established to evaluate the efficacy and safety of tislelizumab combined with radiotherapy as bladder-preserving treatment for HR NMIBC patients unresponsive to BCG. **Methods:** This open-label, single arm phase II study enrolled HR NMIBC patients with BCG-unresponsive papillary tumors (high-grade Ta or T1 tumors without carcinoma in situ). The papillary tumors should be removed all visible lesions by transurethral resection of bladder tumor (TURBT). Within 2 weeks after TURBT, eligible patients received tislelizumab 200 mg in day 1 (D1), every 21 days for eight cycles and a total radiotherapy dose of 60–66 GY in 30–33 fractions over seven weeks. The primary endpoint was disease-free survival (DFS) rate at 12 months (defined as no reappearance of high grade or T1 tumors or clinical stage development after the therapy). Secondary endpoints were bladder-preservation rate, OS and safety. Our study estimated a DFS rate at 12 months was no less than 50% and the study would enroll 32 patients to meet the primary endpoint. **Results:** Between September 4, 2020, and December 11, 2024, 32 patients (26 [81.2%] men and 6 [19.8%] women) who had received a median of eleven (IQR 7–22) previous BCG instillations were enrolled. Patients received a median of 8 cycles (IQR 8–8) of tislelizumab and of radiotherapy doses of 62.0 GY (IQR 62.0–64.0). Median follow-up was 28.8 months (19.7–43.8). The DFS rate at 12 months was 90.6% (95%CI, 79.8%–99.6%), at 24 months was 70.2% (95%CI, 50.1%–83.4%). The bladder-preservation rate at 24 months was 93.2% (95%CI, 75.4%–98.3%). The OS rate at 24 months was 100% (95%CI, 100%–100%). The OS rate at 36 months was 90.5% (95%CI, 67.0%–97.6%). Treatment-related adverse events (TRAEs) occurred in 27 (84.4%) of 32 patients, 7 (21.9%) patients had a grade 3 TRAEs. The most common 3 TRAEs were diarrhea (9.4%), radiocystitis (3.1%), leukopenia (3.1%) and liver function damage (3.1%) without grade 4–5 TRAEs. **Conclusions:** Our final results supported the use of tislelizumab combined with radiotherapy as a promising bladder-preserving therapy for BCG-unresponsive HR NMIBC patients who were ineligible for or decline RC. Clinical trial information: ChiCTR2000035275. Research Sponsor: None.

Prognostic value of post-operative circulating tumor DNA (ctDNA) in real-world treatment and outcomes among patients (pts) with muscle invasive (MIBC) and locally advanced (LA) bladder cancer (BC).

Khilna Patel, Danni Zhao, Erin Fidyk, Eunice Adhiambo Hankinson, Aashay Mahesh Mehta, Matthew Pesavento, Arun Sujenthiran; Flatiron Health, Durham, NC; Flatiron Health, New York, NY; Flatiron Health UK, London, United Kingdom

Background: BC has high recurrence risk despite curative intent surgery and perioperative therapy. As ctDNA guided strategies are investigated in trials, evidence from routine practice is needed to understand treatment decisions and how post-surgery ctDNA status relates to outcomes. This study evaluated real-world survival outcomes and treatment patterns by post-surgery ctDNA status among pts with MIBC/LA BC and assessed prognostic value beyond pathologic response (pCR). **Methods:** This retrospective study used the US-based, EHR-derived deidentified Flatiron Health Research Database (cutoff 08/31/25). Pts with MIBC or LA BC diagnosed on or after January 2015 who underwent surgery and ctDNA testing were included. Pt characteristics were summarized, including ctDNA testing patterns. Adjuvant therapy initiation was described by post-surgery ctDNA status. Real-world overall survival (rwOS) and disease-free survival (rwDFS) were estimated from the date of surgery using Kaplan–Meier methods, stratified by pCR status and post-surgery ctDNA status (results within 90 days post-surgery), and summarized descriptively with landmark survival probabilities. **Results:** Among 388 pts in the study population who underwent surgery and received ctDNA testing, median age at diagnosis was 70 years (IQR: 63.8–75.0); 63% received neoadjuvant therapy, 49% received adjuvant therapy, and 11% had residual disease post-surgery. Use of ctDNA testing increased substantially over time in the study cohort, from 2.6% (10/388) in 2021 to 57% (223/388) in 2025. Of ctDNA-tested pts, 97 pts had evaluable post-surgery ctDNA results (ctDNA+: 10.3% [n=40]; ctDNA–: 14.7% [n=57]). Of these, adjuvant therapy was given to 43% of post-surgery ctDNA+ pts and 35% of ctDNA– pts. The 12-month rwOS (95% CI) was 69.4% (53.8%–89.6%) for ctDNA+ vs 96.5% (91.8%–100.0%) for ctDNA–; 12-month rwDFS (95% CI) was 34.4% (20.8%–56.8%) vs 72.7% (61.2%–86.4%), respectively. Stratified by pCR, outcomes were favorable among pts achieving pCR. Although limited by small sample sizes, ctDNA status appeared to further differentiate prognosis within each stratum, particularly among pts without pCR, where ctDNA+ pts had worse rwOS (43.2% vs 100.0%, $P < .01$) and worse rwDFS (9.9% vs 64.2%, $P = .014$) over time compared with ctDNA– pts. **Conclusions:** Rapid growth in ctDNA testing highlights increasing clinical adoption. Post-surgery ctDNA positivity was linked to worse rwOS/rwDFS in pts with MIBC/LA BC and further stratified prognosis beyond pCR. Importantly, ctDNA may complement pathologic response in identifying pts at highest risk for recurrence and informing post-surgical management. Future work is needed to translate these findings into clinically actionable insights and treatment strategies. Research Sponsor: Flatiron Health, Inc.

Assessing responses to UGN-102 across EORTC recurrence score groups in patients with recurrent low-grade intermediate-risk NMIBC (ENVISION trial).

Sandip M. Prasad, William Huang, Michael J. Louie, Nikky Ugwuoke, Andrew Meads, Brent Burger, Mark Schoenberg, on behalf of The ENVISION Study Group; Morristown Medical Center/Atlantic Health System and Garden State Urology, Morristown, NJ; NYU Langone Urology Associates, New York, NY; UroGen Pharma, Princeton, NJ; The Department of Urology, Montefiore Medical Center: Einstein Campus, Bronx, NY

Background: The ENVISION phase 3 study (NCT05243550) treated patients with recurrent low-grade intermediate-risk non-muscle-invasive bladder cancer (LG-IR-NMIBC) with UGN-102, a reverse thermal hydrogel administered intravesically containing 75 mg mitomycin. Complete response (CR) rate at 3 months was 79.6% (95% confidence interval [CI]: 73.9, 84.5) with a 72.2% (95% CI: 64.1, 78.8) probability of remaining in response 24 months later. The European Organization for Research and Treatment of Cancer (EORTC) recurrence score tables provide estimates of recurrence based on baseline prognostic factors. We conducted a post-hoc analysis of CR and duration of response (DoR) by EORTC recurrence score subgroup. **Methods:** 240 patients with recurrent LG-IR-NMIBC received ≥ 1 dose of UGN-102. CR was assessed at 3 months using cystoscopy, urine cytology testing, and for-cause biopsy. Patients achieving CR entered the follow-up period and are being assessed for recurrence or progression for up to 5 years. CR at 3 months and probability of maintaining CR at 24 months in patients with EORTC recurrence scores of 1–4, 5–9, and 10–17 were calculated. DoR was calculated using the Kaplan–Meier (KM) estimation method. **Results:** The median (range) EORTC recurrence score was 7 (2–13). CR rate at 3 months was 83.9%, 81.2%, and 60.0% for patients with recurrence scores of 1–4 (n=31), 5–9 (n=191), and 10–17 (n=15), respectively. Of the patients with CR at 3 months, 26.9%, 23.9%, and 33.3% (for recurrence scores of 1–4, 5–9, and 10–17) experienced recurrence of LG disease, progression (either in stage or grade), or death by 24 months. The KM estimate of median DoR was not estimable for any group due to the low event rates. **Conclusions:** UGN-102 demonstrated robust complete response rates across all EORTC recurrence score subgroups, including patients with higher baseline recurrence risk. The majority of patients remained recurrence-free at 24 months. Despite the post-hoc design and small subgroup sizes, these findings suggest UGN-102 provides durable and clinically meaningful disease control in recurrent LG-IR-NMIBC. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma, Inc.

	EORTC recurrence score group		
	1–4 N=31	5–9 N=191	10–17 (N=15)
CR at 3 months, n (%)	26/31 (83.9)	155/191 (81.2)	9/15 (60.0)
CRR (95% CI)	83.9 (66.3, 94.5)	81.2 (74.9, 86.4)	60.0 (32.3, 83.7)
Recurrence 24 months ^a , n (%)	7/26 (26.9)	37/155 (23.9)	3/9 (33.3)
Recurrence of LG disease	5/26 (19.2)	27/155 (17.4)	3/9 (33.3)
Progression	0	7/155 (4.5)	0
Death	2/26 (7.7)	3/155 (1.9)	0
Probability of remaining in response at 24 months, %, 95% CI ^b	67.4 (43.2, 83.1)	73.7 (64.6, 80.8)	66.7 (28.2, 87.8)
Median duration of follow up, months, 95% CI ^c	23.29 (23.03, 23.92)	23.72 (23.66, 23.92)	23.90 (23.72, NE)

^a24 months after 3-month CR.

^bCalculated using the KM method, with Brookmeyer–Crowley CIs.

^cEstimated using reverse KM method. CI, confidence interval; CRR, complete response rate.

Patient experiences with UGN-102 for recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC): Insights for shared decision making.

Ruchika Talwar, Rahul Dhanda, Anagha Nadkarni, Nikky Ugwuoke, Victoria Michelle Tsurutis, Michael J. Louie, Charles Peyton; Department of Urology, Vanderbilt University Medical Center, Nashville, TN; UroGen Pharma, Princeton, NJ; Urologic Oncology, University of Alabama at Birmingham, Birmingham, AL

Background: Recurrent LG-IR-NMIBC can be managed using various approaches, including repeat transurethral resection of bladder tumor (TURBT) and non-surgical intravesical therapies. One option is UGN-102, a reverse thermal hydrogel containing 75mg mitomycin. Given LG-IR-NMIBC tends to recur, understanding patients' experiences/preferences across management strategies is essential to support clinical shared decision making. **Methods:** The ENVISION study (NCT05243550) assessed patient-reported outcomes via EORTC-QLQ-NMIBC24. Patients with biopsy-confirmed LG-IR-NMIBC and ≥ 1 previous NMIBC episode at baseline had 6 once-weekly intravesical instillations of UGN-102 in an outpatient setting. 32 US-based patients had semi-structured prospective phone interviews that compared experiences of prior TURBT (at enrollment) vs UGN-102 at 3 months. **Results:** 232 patients were included; 94.8% received all 6 doses of UGN-102. Mean change from baseline (CfB) scores at 3- and 12-months post-treatment did not reach minimal clinically important difference (MCID) thresholds for any of the EORTC-QLQ-NMIBC24 domains (Table). Patients perceived more interference with routines/responsibilities with TURBT vs UGN-102, similar urinary symptoms, expressed concern regarding more bleeding with TURBT, and would recommend UGN-102 as a less invasive, painful, and time-consuming procedure than TURBT. A small number of patients preferred surgery as a 1-day procedure vs 6 weekly intravesical instillations. **Conclusions:** UGN-102 maintained stable quality-of-life scores across NMIBC24 domains and was generally preferred by patients over surgical resections. These important insights support shared decision making, enabling clinicians to discuss trade-offs between procedural convenience and treatment invasiveness in recurrent LG-IR-NMIBC management. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma, Inc.

EORTC-QLQ-NMIBC24 domain	MCID	Baseline, mean (SD) n	3-month CfB, mean (SD) n	12-month CfB, mean (SD) n
Urinary symptoms	6.34	13.7 (14.50) 231	0.8 (13.30) 217	-0.6 (10.71) 154
Malaise	4.37	4.0 (8.79) 231	0.2 (10.57) 217	1.2 (9.55) 154
Intravesical treatment issues	9.38	12.8 (18.74) 231	-0.8 (20.14) 217	0.2 (20.34) 154
Future worries	11.08	35.6 (22.49) 231	-4.1 (21.71) 217	-7.1 (22.84) 154
Bloating and flatulence	7.59	9.2 (15.35) 231	1.1 (16.24) 217	0.8 (15.52) 154
Risk of contaminating partner	13.66	10.9 (23.74) 141	-1.6 (17.45) 106	-7.5 (20.78) 67
Female sexual problems	12.87	9.6 (22.04) 45	-2.1 (18.81) 32	-3.5 (15.29) 19
Male sexual problems	16.29	21.9 (32.77) 144	1.2 (23.71) 134	0 (26.89) 94
Sexual intimacy	8.69	8.0 (17.27) 142	1.3 (22.35) 103	2.9 (20.55) 68
Sexual function	10.61	79.4 (25.01) 231	4.0 (15.25) 218	4.1 (16.97) 154
Sexual enjoyment	11.64	60.5 (33.11) 140	8.0 (25.23) 104	10.4 (29.71) 67

SD, standard deviation. A positive CfB indicates worsening across all scales/items.

Influence of low-coverage whole-genome sequencing–based urinary tumor fraction and chromosomal instability on recurrence risk stratification in systemic immunotherapy-treated non–muscle–invasive bladder cancer.

Yunkai Qie, Zihan Xue, Liliang Li, Shan Liang, Jiazeng Zhao, Guoqiang Han, Chong Shen, Zhouliang Wu, Qian Ziliang Sr., Hailong Hu; The Second Hospital of Tianjin Medical University, Tianjin, China; Daqing Oilfield General Hospital, Daqing, China; Hongyuan Biotech, Suzhou, China

Background: Urinary tumor DNA (utDNA) is increasingly explored for prognostic assessment in bladder cancer, but most studies rely on a simple positive/negative classification, and its prognostic value in patients receiving systemic immune checkpoint inhibitors (ICIs) remains unclear. Low-coverage whole-genome sequencing (LC-WGS) of urine enables low-cost quantitative assessment of tumor fraction (TF) and chromosomal instability (CIN), providing richer molecular information than conventional binary utDNA status. We evaluated whether LC-WGS–derived TF and CIN improve prognostic stratification in ICI–treated high- and very high-risk non–muscle–invasive bladder cancer (NMIBC). **Methods:** Patients with high- or very high-risk NMIBC were enrolled in a prospective cohort treated with ICI tislelizumab plus low-dose nab-paclitaxel. Pretreatment urine samples were collected and analyzed using LC-WGS to derive TF and CIN. Clinicopathologic variables were collected at baseline. The primary endpoint was 2-year recurrence-free survival (RFS). Prediction models were constructed using clinicopathologic features (tumor size, number, concomitant carcinoma in situ, lymphovascular invasion) alone and in combination with TF and CIN. **Results:** A total of 35 patients were included. After a median follow-up of 27.3 months, 11 patients experienced disease recurrence. Models based on clinicopathologic features alone demonstrated limited discrimination for 2-year RFS (AUC = 0.61). Higher urinary TF and CIN were significantly associated with increased recurrence risk (TF: HR 2.18, 95% CI 1.29–3.97, $p = 0.004$; CIN: HR 2.74, 95% CI 1.41–5.32, $p = 0.002$). Incorporation of TF improved discrimination (AUC = 0.71), and further addition of CIN achieved the highest performance (AUC = 0.80; Δ AUC = 0.19 vs clinical model, $p = 0.01$). Patients classified as high molecular risk based on combined TF and CIN had significantly lower 2-year RFS than those at low molecular risk (HR 3.92, 95% CI 1.62–9.48, $p = 0.002$). Notably, the molecular-only model incorporating TF and CIN demonstrated discrimination comparable to the clinicopathologic–integrated model (AUC = 0.79 vs 0.80, $p = 0.68$), suggesting that urinary genomic features alone may provide sufficient information for recurrence risk stratification in this setting. **Conclusions:** Urinary TF and CIN derived from cost-effective LC-WGS substantially improved recurrence risk stratification beyond conventional tumor characteristics in NMIBC patients treated with systemic immunotherapy. These findings suggest that urine-based molecular profiling may offer a practical and scalable complement to conventional clinicopathologic risk assessment for baseline risk stratification and post-therapy management. Research Sponsor: None.

UTOPIA: A phase 3 trial of UGN-103, an intravesical mitomycin reverse thermal hydrogel, in recurrent low-grade intermediate-risk non-muscle invasive bladder cancer.

Abhishek Srivastava, Egils Vjaters, Hristos Z. Kaimakliotis, Sandip M. Prasad, Madlen Malinowski, Michael J. Louie, Sebastian Mirkin, Nikky Ugwuoke, Brent Burger, Mark Schoenberg, on behalf of the UTOPIA Study Group; Carolina Urologic Research Center, Myrtle Beach, SC; P. Stradiņš Clinical University Hospital, Riga, Latvia; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Morristown Medical Center/Atlantic Health System and Garden State Urology, Morristown, NJ; UroGen Pharma, Princeton, NJ; The Department of Urology, Montefiore Medical Center: Einstein Campus, Bronx, NY

Background: Management of recurrent low-grade (LG), intermediate-risk (IR) non-muscle invasive bladder cancer (NMIBC) remains challenging due to frequent recurrence following standard surgical management with transurethral resection of bladder tumor (TURBT). UGN-102 is an intravesical mitomycin reverse thermal hydrogel, approved by the Food and Drug Administration for treatment of adults with recurrent LG-IR-NMIBC based on the Phase 3 ENVISION trial demonstrating a complete response (CR) rate of 80% (95% confidence interval [CI]: 74, 85) at 3 months, with an 82% (95% CI: 76, 87) probability of remaining in response 12 months from initial CR. UGN-103 is a novel formulation of UGN-102 developed to simplify drug preparation and shorten manufacturing time. **Methods:** UTOPIA (NCT06331299) is an ongoing, multicenter, single-arm, Phase 3 study evaluating UGN-103 as primary treatment for adults with recurrent LG-IR-NMIBC. Eligible patients provided written informed consent and received six once-weekly intravesical instillations of UGN-103 (mitomycin 75 mg in 56 mL admixture). Disease assessment was performed 3 months after start of treatment. Patients with no detectable disease entered a follow-up period, with evaluations every 3 months until recurrence, progression, death, or completion of follow-up (12 months after the 3-month visit). The primary endpoint was CR rate (defined as the proportion of patients assessed as having no evidence of disease at the 3-month visit) based on cystoscopy, for-cause biopsy, and urine cytology. Secondary endpoints include durability of response, safety and tolerability, and pharmacokinetics. Data cut off: September 3, 2025. **Results:** A total of 99 patients received ≥ 1 instillation of UGN-103; of these, 97% (n=96) received all 6 instillations. At baseline, median patient age was 71 years (range 46, 93), with 78% (n=77) being ≥ 65 years old. Most patients were male (72%; n=71) and 99% (n=98) were White. Most patients had multiple tumors (90%; n=87), with the longest tumor diameter being ≤ 3 cm in 96% (n=93). At 3 months, 77 of 99 patients in the intent-to-treat population achieved CR (CR rate: 78% [95% CI: 68, 86]). Non-CR outcomes included residual disease in 16% (n=16) and progression to high-grade disease in 4% (n=4). Two (2%) patients had missing/indeterminate responses. Treatment-emergent adverse events (TEAEs) were reported in 60% of patients (n=59), with the most common TEAE ($\geq 10\%$) being dysuria (19%; n=19). Two (2%) patients had a total of 3 serious TEAEs, including atrial fibrillation, osteoarthritis, and respiratory failure; none were treatment related. No TEAE led to death. **Conclusions:** UGN-103 demonstrated a safety and efficacy profile similar to that observed with UGN-102 in patients with recurrent LG-IR-NMIBC, supporting continued evaluation of UGN-103 as an intravesical treatment option. Clinical trial information: NCT06331299. Research Sponsor: UroGen Pharma, Inc.

Preliminary results of a phase II study to evaluate the efficacy and safety of disitamab vedotin (RC48-ADC) in combination with radiotherapy for adjuvant therapy in upper tract urothelial carcinoma.

Zihao Tao, Chunru Xu, Xiaoying Li, Qi Tang, Xuesong Li; Department of Urology, Peking University First Hospital, Peking University, Beijing, China; Department of Urology, Peking University First Hospital, Beijing, China; Department of Radiation Oncology, Peking University First Hospital, Peking University, Beijing, China

Background: Although postoperative platinum-based adjuvant chemotherapy improves disease-free survival (DFS), many upper tract urothelial carcinoma (UTUC) patients (pts) were ineligible for cisplatin after radical nephroureterectomy (RNU). UTUCs did not seem to benefit from adjuvant immunotherapy. Previous evidence demonstrated adjuvant radiotherapy improves cancer-specific survival in HR UTUCs. Further exploration of alternative adjuvant treatment strategies is needed. This study aims to evaluate the therapeutic potential of RC48-ADC in combination with radiotherapy in HER2 overexpressing UTUCs. **Methods:** This is an open-label, phase II, non-randomised study to evaluate the efficacy and safety of disitamab vedotin (RC48-ADC), a humanized anti-HER2 antibody, in combination with radiotherapy as a novel adjuvant therapy strategy in UTUC. We recruited cisplatin-intolerant pts with HER2-overexpressing (Immunohistochemistry, IHC 2+, 3+) UTUC after nephroureterectomy staged as pT2NoMo with high-grade/multifocal disease/positive surgical margin, pT3-4 No Mo or pTany N1-2 Mo. Pts who declined any adjuvant therapy were assigned to the surveillance group. Pts in adjuvant therapy group received RC48-ADC (2.0 mg/kg D1 Q2W, 6 months) and radiotherapy (45-50Gy/25f/5w, lymphatic drainage regions; 62.5Gy/25f/5w, enlarged lymphnode). The therapy was initiated within 90 days of surgery. The primary end point was DFS. Secondary end points were overall survival (OS), metastasis-free survival (MFS), local-recurrence free survival (LRFS) and safety. The trial is registered with ClinicalTrials.gov, NCT06210490. **Results:** As of January 2026, 54 patients out of the planned 60 pts have been enrolled in the study. Thirty pts were assigned to adjuvant therapy group and 24 in surveillance. In therapy group, 17 pts completed adjuvant therapy, while 13 pts were undergoing treatment. At a median follow-up of 12.4 months, one recurrence was observed in the therapy group, while 9 patients in surveillance experienced recurrence. The 1-year disease-free survival rates were 95% (95% CI 85.9-100) in the adjuvant therapy group and 69.6% (95% CI 53.1-91.2) in the surveillance group. As of now, the most common ($\geq 20\%$) treatment-related adverse events (TRAEs) were peripheral sensory neuropathy (40%), increased AST (28%), asthenia (28%) and alopecia (20%). Grade ≥ 3 TRAE was observed in 2 patients (8%), the patients experienced gastrointestinal hemorrhage and peripheral sensory neuropathy, respectively. **Conclusions:** This study is the first to evaluate the efficacy and safety in adjuvant treatment of ADC plus radiotherapy in UTUCs. The combination of RC48-ADC and radiotherapy as a new adjuvant therapy demonstrated a tolerable safety profile in pts with HER2-overexpressing UTUC. Clinical trial information: NCT06210490. Research Sponsor: RemeGen.

Adjuvant nivolumab in high-risk muscle-invasive urothelial carcinoma: Real-world evidence from the SOGUG-NIADY study of the Spanish Oncology Genitourinary Group (SOGUG).

Sara Perez Ramirez, Aurea Molina Diaz, Imanol Martinez, Aina Iranzo Sabater, Esther Martínez Ortega, Rebeca Lozano, Teresa Bonfill, Julio Lambea Sorrosal, Mireia Martinez-Kareaga, Sara Cerezo Gonzalez, Martín Oré-Arce, Iria Gonzalez Maeso, Alberto Torres Zurita, Edinson Caviedes Sanchez, Francisco Zambrana, Amaia Morena, Almudena Martin, Ana Vacas, Sara Blasco Mollá, Francesc Pons Valladares; Hospital Gregorio Marañón, Madrid, Spain; Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; Medical Oncology Department, University Hospital Fundación Jiménez Díaz, IIS-FJD, Madrid, Spain; Hospital Universitario de La Ribera, Valencia, Spain; Hospital Universitario de Jaén, Jaén, Spain; Complejo Asistencial Universitario de Salamanca; Institute for Biomedical Research of Salamanca (IBSAL), Salamanca, Spain; Hospital Universitari Parc Taulí, Barcelona, Spain; Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; Hospital Universitario de Araba-Txagorritxu, Vitoria, Spain; Hospital Universitario la Mancha Centro, Toledo, Spain; Hospital Universitario del Vinalopó, Alicante, Spain; Hospital Son Llatzer, Mallorca, Spain; Hospital Universitario Virgen Macarena, Sevilla, Spain; Hospital Universitario Príncipe de Asturias, Asturias, Spain; Hospital Universitario Infanta Sofía, Madrid, Spain; Hospital Universitario Galdakao Usansolo, Bilbao, Spain; Hospital Universitario Infanta Leonor, Madrid, Spain; Hospital Universitario de Jerez de la Frontera, Cádiz, Spain; Hospital de Sagunto, Valencia, Spain; Hospital Universitari General de Catalunya, Barcelona, Spain

Background: Adjuvant nivolumab significantly improved disease-free survival (DFS) in patients (pts) with high-risk muscle-invasive urothelial carcinoma (MIUC) after radical surgery in the phase III CheckMate-274 trial. Based on these results, since August 2023, the Spanish National Health System reimburses postoperative nivolumab in high-risk, positive programmed death ligand 1 (PDL1) MIUC. The aim of the PrInCIS-NIADY study was to assess the effectiveness and safety of adjuvant nivolumab in real-world clinical practice after its approval in Spain. **Methods:** PrInCIS is a nationwide multicentre, non-interventional epidemiological study with retrospective patient inclusion and prospective follow-up. The NIADY cohort included pts with high-risk PDL1+ MIUC treated with adjuvant nivolumab in routine practice, was conducted across 65 hospitals belonging to the Spanish Oncology Genitourinary Group (SOGUG) in 16 Spanish regions. Baseline characteristics, treatment patterns, safety, and outcomes were analysed and compared against CheckMate-274. **Results:** A total of 395 evaluable pts were included, 95.7% were PD-L1 positive. Median age was 69.5 years, (74.9% aged ≥ 65 years); 91.4% had bladder cancer and 8.6% had upper tract disease. Predominant histology was urothelial carcinoma (79.2%). 51.2% pts received neoadjuvant platinum-based chemotherapy (NACHT) (48.9% cisplatin vs. 2.3% carboplatin) (Table). With a median follow-up of 13 months, 27.3% of pts had disease recurrence. Treatment after recurrence was platinum-based ChT in 8.8% and enfortumab vedotin in 6.6% of pts. Median DFS and overall survival (OS) were not reached. The estimated 18-month DFS and OS probability were 65.6% and 78.3% respectively. Nivolumab was well-tolerated: Treatment delays or dose reductions occurred in 37.3% of pts. Most common ($>10\%$) grade 1–2 immune-related adverse events were fatigue, pruritus and diarrhea, while grade 3–4 toxicity was infrequent ($>1\%$), mainly consisting in hepatic enzyme and creatinine elevation. **Conclusions:** Outcomes and effectiveness of adjuvant nivolumab in this large Spanish real-world cohort were consistent with the Checkmate-274 results, with a manageable safety profile despite an older population. In spite of short-term follow-up, these findings externally validate the results of the pivotal trial reinforcing the role of adjuvant nivolumab in daily clinical practice for high-risk MIUC. Research Sponsor: SOGUG: Spanish Oncology Genitourinary Group.

Patient characteristics.

Characteristics	CHECKMATE-274 (N=353)	NIADY (N=395)
Age. Mean (range)-yr	65.3 (30-92)	69.5 (35-88)
Sex. Male / Female	75.1 / 29.9 %	81.8 / 19.2 %
ECOG 0-1 / >2	98 / 2 %	96.7 / 3.3 %
Bladder/Upper tract	79 / 21 %	91.4 / 8.6 %
Pure urothelial / mixed histology	59.7 / 40.3 %	79.2 / 20.7 %
NACHT cisplatin / carboplatin	43.3 / NA %	48.9 / 2.3 %
pT2-4a N0	52.2 %	64.3 %
pT4b o N+	47.3 %	35.7 %
PDL1+ $\geq 1\%$	39.7 %	95.7 %

Magnitude and timing of clinical benefit associated with pathologic complete response in perioperative muscle-invasive bladder cancer: A reconstructed IPD analysis of NIAGARA trial.

Andrea Malgeri, Alessio Cortellini, Linda Cerbone, Brigida Maiorano, Maria Bassanelli, Grazia Sirgiovanni, Claudia Mosillo, Fabio Calabrò; Medical Oncology 1, IRCCS National Cancer Institute Regina Elena, Rome, Italy; Campus Bio-Medico University of Rome, Rome, Italy; Department of Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy; Medical Oncology 1, IRCCS Regina Elena National Cancer Institute, Rome, Italy

Background: Pathologic complete response (pCR) is widely used as an early efficacy endpoint in neoadjuvant or perioperative bladder cancer trials. However, formal surrogacy analyses linking pCR to long-term clinical outcomes are lacking. In particular, the magnitude and timing of clinically meaningful benefit associated with pCR remain poorly defined. We aimed to quantify the absolute benefit and temporal emergence of event-free survival (EFS) and overall survival (OS) associated with pCR in NIAGARA trial. **Methods:** Individual patient data (IPD) were reconstructed from the most recent publicly available Kaplan-Meier curves of the NIAGARA trial, including stratification by pCR and non-pCR status for each treatment arm. The primary analysis compared outcomes between pCR and non-pCR patients within each treatment arm. Restricted mean survival time differences (Δ RMST) were estimated at 24 months for EFS and 36 months (mo) for OS. Time to benefit (TTB) was defined as the earliest time point at which Δ RMST reached ≥ 1 mo for EFS and ≥ 2 mo for OS. Exploratory analyses compared outcomes within pCR patients and within non-pCR patients between treatment arms, to explore whether the clinical benefit associated with pCR is purely prognostic or reflects treatment-related modulation within pathological response strata. **Results:** At 24 months, pCR was associated with a large and early EFS benefit across treatment arms. Among patients receiving durvalumab + cisplatin-gemcitabine (CG), pCR was associated with a Δ RMST of +5.87 mo (95% CI 4.78–6.96; $p < 0.0001$) compared with non-pCR, with a TTB of 9 mo. Similar results were observed in the CG arm (Δ RMST of +5.63 mo, 95% CI 4.49–6.77; $p < 0.0001$), with a TTB of 9 mo. At 36 months, pCR was also associated with a substantial OS benefit. In the durvalumab + CG arm, pCR was associated with a Δ RMST of +5.32 mo (95% CI 3.89–6.74; $p < 0.0001$) versus non-pCR, with a TTB of 22 mo. Comparable findings were observed in the CG arm (Δ RMST +5.89 mo, 95% CI 4.30–7.47; $p < 0.0001$), and a TTB of 20 mo. In exploratory analyses, no significant EFS or OS differences were observed between treatment arms among pCR patients (Δ RMST < 1 month), with a TTB of 38 mo for EFS and not reached within 60 mo for OS. Among non-pCR patients, treatment-related differences were similarly modest (Δ RMST ~ 1 month), with delayed TTB (19 mo for EFS and 50 mo for OS). **Conclusions:** Using reconstructed IPD from NIAGARA, pCR identifies a large, early EFS benefit and a later OS benefit, informing, in the absence of formal surrogacy validation, a quantitative and temporal clinical interpretation of pCR. In contrast, no additional treatment-related survival benefit was observed within pCR or non-pCR subgroups, raising the hypothesis that survival differences may be largely attributable to pCR rather than to treatment-related modulation within response strata. Research Sponsor: None.

Progress of phase II study of MVR-T3011, an IL-12/anti-PD-1 armed oncolytic HSV-1, in high-risk BCG-unresponsive CIS and papillary NMIBC.

Dingwei Ye, Junlong Wu, Mingming Zhang, Dashuang Xu, Xu Jin, Yonghong Liu, Xiaoqing Chen, Grace Zhou; Fudan University Shanghai Cancer Center, Shanghai, China; ImmVira Pharma Co. LTD, Suzhou, China

Background: MVR-T3011 is a novel Phase II oncolytic immunotherapy candidate based on herpes simplex virus type 1 (HSV-1). It combines potent tumor lysis with co-expression of anti-PD-1 antibody and IL-12. MVR-T3011 is being evaluated as monotherapy in patients with non-muscle invasive bladder cancer (NMIBC), including both BCG-unresponsive and BCG-naïve populations. Herein, we report the latest Phase II results of MVR-T3011 in BCG-unresponsive carcinoma in situ (CIS) and papillary NMIBC. **Methods:** In this ongoing trial, MVR-T3011 is administered intravesically in 50 mL without prewash. This simplified procedure utilizes the virus's natural ability to bind to glycosaminoglycans (GAGs) on the urothelial surface as attachment receptors. Patients were assigned to two groups: 1) 2×10^9 PFU, administered weekly for 12 weeks during the induction phase, followed by maintenance treatment every 2 weeks; 2) 1×10^{10} PFU, administered weekly for 6 weeks for induction, then every 3 weeks of treatment for maintenance. Both continued for up to 2 years. Efficacy was assessed every 3 months via cystoscopy, cytology, biopsy, and imaging. Primary endpoints were complete response rate (CRR) for CIS and recurrence-free survival (RFS) for papillary disease. The safety was fully evaluated. **Results:** As of Dec 31, 2025, a total of 43 patients were enrolled, 14 with CIS and 29 with Papillary. Among 13 evaluable CIS patients, 7 were treated at 2×10^9 PFU dose level, achieving 6-month CRR of 71.4% (5/7), 3 patients maintained CR for 12 months, and 1 patient remained in CR for 18 months. 6 patients treated at 1×10^{10} PFU dose level, all achieved complete responses, with 100% CRR at 3 months (6/6), 6 months (5/5), and 9 months (3/3). Among 26 evaluable papillary patients, 16 were treated at the 2×10^9 PFU dose level. The RFS rate was 80.8% (95% CI: 51.4–93.4) at 6 months, 74.0% (95% CI: 44.6–89.4) at both 12 and 15 months, and 64.8% (95% CI: 34.0–84.0) at both 18 and 21 months. 10 patients treated at 1×10^{10} PFU dose level, the 3-month and 6-month RFS rates were both 88.9% (95% CI: 43.3–98.4). Assessment of the safety data revealed that most treatment-related adverse events (TRAEs) were grade 1. Common events included hematuria (25.0%), urinary tract infection (11.4%), proteinuria (9.1%), pollakiuria (6.8%), and rash (6.8%; immune-related). Only two grade 3 TRAEs were reported, both of which were urinary tract infections. No higher-grade TRAE or SAE occurred. **Conclusions:** MVR-T3011 is being evaluated as mono or combination therapy across multiple solid tumors. In this study, MVR-T3011 demonstrates suitability for intravesical administration, plus promising efficacy and a favorable safety profile. Durable complete responses were observed in CIS patients and encouraging 12-month RFS rates in papillary disease. These findings support its potential as a bladder-sparing option for BCG-unresponsive NMIBC. Clinical trial information: NCT06427291. Research Sponsor: None.

Bulumtaturg fuvedotin (BFv; 9MW2821) plus toripalimab in perioperative patients with muscle-invasive bladder cancer (MIBC): Results of cohort A from a phase 2 study.

Zhuowei Liu, Shusuan Jiang, Minfeng Chen, Zhisong He, Jingming Dong, Peipei Wang, Shuhai Wang; Sun Yat-sen University Cancer Center, Guangzhou, China; Hunan Cancer Hospital, Changsha, China; Xiangya Hospital of Central South University, Changsha, China; Department of Urology, Peking University First Hospital, Institute of Urology, Peking University, Beijing, China; Mabwell (Shanghai) Bioscience Co., Ltd., Shanghai, China

Background: Radical cystectomy with pelvic lymph node dissection (RC+PLND) has always been the standard treatment for MIBC. Perioperative treatment, especially cisplatin-based neoadjuvant therapy, could reduce the risk of tumor recurrence effectively and prolong the survival of patients. BFv, a novel Nectin-4 antibody-drug conjugate, combined with toripalimab, has demonstrated promising efficacy and safety profile in advanced urothelial cancer patients. This provides possibilities for the perioperative treatment of MIBC. Here we report the preliminary results of BFv plus toripalimab in patients with perioperative MIBC (cohort A). **Methods:** Patients with MIBC (cT2-4aN0-1M0) can be enrolled in cohort A. Eligible patients will receive BFv plus toripalimab for 4 cycles in neoadjuvant stage, and then proceed with RC+PLND. After surgery, patients will receive BFv plus toripalimab for 6 cycles and toripalimab only for the next 11 cycles in the adjuvant stage. The primary endpoint was pathological complete response (pCR). Main secondary endpoints were pathological downstaging (PDS) rate and disease-free survival (DFS), overall survival (OS) and safety. **Results:** As of 4 Jan 2026, 32 patients were enrolled in the cohort A. 7 patients had completed neoadjuvant therapy and 6 of them were performed with RC+PLND. One patient achieved CR in the neoadjuvant stage and refused to undergo the surgery. pCR rate was 66.7% (4/6, 95%CI 22.3-95.7), PDS rate was 83.3% (5/6, 95%CI 35.9-99.6). DFS and OS were not mature. Safety profile was consist with previous study. No new safety signals of BFv or toripalimab were observed in this study. **Conclusions:** This study showed remarkable preliminary efficacy of BFv plus toripalimab in perioperative patients with MIBC. It may offer a new choice for MIBC patients and deserve to be further investigation. Clinical trial information: NCT07314723. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

Survival and treatment patterns of patients with metastatic urothelial cancer in France: Results of a cohort study using the French National Healthcare database (SNDS).

Philippe Barthelemy, Mairead Kearney, Laura Luciani, Benoit Van Hille, Laurent Paret, Reyhan Hasanova, Faysoil Fouad, Vanessa Rascon Velasco, Isabelle Durand-Zaleski, Constance Thibault; Institut de Cancérologie Strasbourg Europe, Strasbourg, France, Strasbourg, France; The Healthcare Business of Merck KGaA, Darmstadt, Germany; Merck Santé S.A.S., an Affiliate of Merck KGaA, Darmstadt, Germany; Oracle France, Paris, France; Université de Paris, CRESS, Paris, France; Hôpital Européen Georges Pompidou, Institut du Cancer Paris CARPEM, AP-HP Centre, Université de Paris Cité, Paris, France

Background: Despite the increasing number of available treatment options, metastatic urothelial cancer (mUC) remains a challenging disease, characterized by high mortality and substantial rates of undertreatment worldwide. In this study, we aimed to describe treatment patterns and survival among patients with mUC in France. **Methods:** This retrospective study included adult patients with incident mUC between January 2017 and December 2023. The overall study cohort was divided into two subcohorts: treated, defined as initiating any systemic treatment within 120 days after index date and untreated (defined as not initiating any treatment within 120 days after index date). The index date was defined as diagnosis (first recorded ICD-10 code for metastasis) or start of systemic anticancer treatment. Overall survival (OS) was estimated using Kaplan-Meier method, calculated from the index date for the overall cohort and untreated subcohort, and from the initiation of first line (1L) treatment for the treated subcohort. Baseline characteristics including sex, age, and age-adjusted Charlson Comorbidity index (CCI) were compared between treated and untreated subcohorts using χ^2 and Wilcoxon tests. **Results:** The study included 24,912 patients, male (77.8%), mean (SD) age was 75 (11) yrs, and median (IQR) age-adjusted CCI was 4 (2-5). Median (IQR) follow-up was 2.5 (1-10) months. Mortality was 90.8%, primarily due to malignant tumors (88.6%) among the recorded causes of death. Overall, 1L treatment was initiated in 10,562 pts (42.4%), with increasing annual rates from 2017 (38%) to 2023 (47%). Chemotherapy was the predominant 1L treatment (75.4%) followed by immune-oncology (IO) agents (24.5%). Of 7,960 pts receiving 1L chemotherapy, 4,193 (53%) did not receive any further treatment, and 2,184 (27%) patients received chemotherapy, 1,359 (17%) IO, and 224 (3%) antibody-drug conjugates in second line. Mean (SD) time from index date to 1L initiation was 18 (25) days and mean (SD) duration of 1L was 101 (155) days. Median OS was 2.5 (95% CI 2.4-2.6), 7.6 (7.4-7.8) and 1.1 (1.1-1.1) months for the overall cohort, treated and untreated subcohorts, respectively. It decreased with higher CCI scores: from 3.99 months for patients with CCI 0 to 1.54 months for those with CCI ≥ 5 . Sex, age and CCI were significantly different between treated and untreated patients ($p < 0.0001$). **Conclusions:** This nationwide population-based study showed that more than half of patients with mUC treated in real-world clinical practice in France did not receive 1L systemic treatment. Untreated individuals were mainly elderly, male, comorbid, and experienced poor survival. These findings underscore the importance of the early utilization and optimization of available therapies to improve outcomes, especially among untreated patients with mUC. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Real-world effectiveness of disitamab vedotin plus PD-1 inhibitor versus platinum-based chemotherapy as postoperative adjuvant therapy in high-risk upper tract urothelial carcinoma: A comparative study.

Yudong Cao, Mingjian Ruan, Shuo Wang, Jia Liu, Qiang Zhao, Xingxing Tang, Jinchao Ma, Chen Lin, Peng Du; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Urology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Currently, gemcitabine–platinum combination chemotherapy represents the standard adjuvant regimen following radical surgery for high-risk upper tract urothelial carcinoma (UTUC), as it reduces the risk of disease progression in approximately half of all patients. Nevertheless, a substantial proportion of patients are ineligible for this standard regimen due to post-surgical complications like renal insufficiency. Disitamab vedotin (DV), an antibody–drug conjugate targeting HER-2, has recently been shown to yield superior outcomes in advanced urothelial carcinoma when combined with PD-1 inhibitor immunotherapy. Therefore, based on real-world data, this study aims to evaluate the efficacy of the DV plus PD-1 inhibitor versus standard gemcitabine–platinum chemotherapy in the operative adjuvant treatment of UTUC. **Methods:** A retrospective cohort analysis was conducted using data from UTUC patients at Peking University Cancer Hospital between January 2015 and June 2025. The study included UTUC patients diagnosed as pT_{2–4a}N₀M₀, who received either 4–6 cycles of DV combined with PD-1 inhibitors or gemcitabine–platinum (cisplatin or carboplatin selected based on postoperative renal function) combination chemotherapy. The primary endpoint was disease-free survival (DFS), the key secondary endpoint was treatment-related adverse events (TRAEs). **Results:** A total of 105 UTUC patients were enrolled, with a median follow-up of 45.7 months. Of these, 34 patients were treated with DV combined with PD-1 inhibitors (DV group), and 71 patients received chemotherapy. Compared with chemotherapy, the DV plus PD-1 inhibitor significantly prolonged DFS, with a hazard ratio of 0.29 (95% CI 0.09–0.98; P = 0.047). The estimated 3-year DFS rates were 83.1% (95% CI 66.8–100.0) in the DV group and 64.9% (95% CI 54.3–77.7) in the chemotherapy group. Regarding safety, grade ≥ 3 TRAEs occurred more frequently in the chemotherapy group than in the DV group (36.6% vs. 12.9%), mainly comprising hematologic toxicities. **Conclusions:** Disitamab vedotin combined with PD-1 inhibitor immunotherapy might improve DFS compared with standard chemotherapy as adjuvant therapy for UTUC. Supported by favorable efficacy and safety outcomes, this combination represents a promising postoperative treatment option. Research Sponsor: None.

Participants' and tumour characteristics.				
	Total (n=105)	DV group (n=34)	Chemotherapy group (n=71)	P value
Age(years) , median(IQR)	63 (56.5-63)	65 (57-69)	63 (56-70)	0.848
Sex, n (%)				
Male	56 (53.3)	16 (47.1)	40 (56.3)	0.372
Female	49 (46.7)	18 (52.9)	31 (43.7)	
Pathological T stage				0.453
pT2	37 (35.2)	11 (32.4)	26 (36.6)	
pT3	58 (55.2)	18 (52.9)	40 (56.3)	
pT4	10 (9.5)	5 (14.7)	5 (7.0)	
Nodal stage				0.225
N0	95 (90.5)	33 (97.1)	62 (87.3)	
N1	5 (4.8)	0 (0)	5 (7.0)	
N2	5 (4.8)	1 (2.9)	4 (5.6)	

Real-world treatment patterns and clinical outcomes among US patients with non-muscle invasive bladder cancer (NMIBC) during the BCG shortage.

Suzanne Biehn Merrill, Manami Bhattacharya, Weiyan Li, Helen Marshall, Etkin Gurcan, Connor Sweetnam, Megan Milos, Monika A. Izano; Colorado Urology Group, Lakewood, CO; AstraZeneca, Gaithersburg, MD; AstraZeneca, Cambridge, United Kingdom; AstraZeneca Pharmaceuticals LP, Gaithersburg, MD; N-Power Medicine, Redwood City, CA

Background: Bladder cancer is diagnosed in 80,000 US patients (pts) annually; 70% present as non-muscle invasive (NMIBC). Guidelines are risk-based; treatment for high risk (hr) disease includes tumor resection (TURBT) and intravesical therapy, commonly Bacille Calmette Guérin (BCG). Delivery of indicated treatment remains challenged, especially by ongoing (acutely since 2017) BCG shortages. We describe recent real-world (rw) patient characteristics, treatments (BCG, TURBT use), and clinical outcomes for NMIBC pts by risk group. **Methods:** We analyzed demographic, clinical and treatment data from electronic health records in N-Power Medicine's Real-World Analytical Dataset, largely based in the Midwest. Adults diagnosed with NMIBC between 1/2017 – 6/2022 were included and followed through 2022. Pts were classified as hr (Y/N) by AUA definition. Kaplan-Meier (KM) curves estimated BCG maintenance (MTX) duration, rw MIBC and metastatic free survival (modified PFS), cystectomy free survival (CFS), overall survival (OS), and recurrence free survival (RFS). Logistic and Cox regression was used to identify predictors of MTX start and discontinuation among hr pts including demographics, diagnosis year, smoking status, Charlson comorbidity index (CCI) and physician specialty. **Results:** Among 3,516 NMIBC pts (median age at diagnosis 72 years), 2,634 (75%) had hrNMIBC; most were non-Hispanic White (88%) and male (75%). Over a median follow-up of 2.7 years, 29% of hrNMIBC pts received BCG induction (IDX); 12% received BCG MTX and median MTX duration was 7.7 months (95% confidence interval [CI]: 6.8–9.2). For hr pts who received IDX, those diagnosed in 2019–2020 were less likely to initiate MTX (2019 vs 2017: OR 0.4; 95% CI [0.2–0.7], 2020 vs. 2017: OR 0.6 CI [0.4–1.0]). Hr pts with higher CCI (>2 vs 0: HR 2.2 [1.2–4.2]) were more likely to discontinue MTX. Most (95%) BCG recipients received no other therapy after BCG. Nearly all pts (>99%) received TURBT. Clinical outcomes (rwmPFS, rwCFS, rwOS) were less favorable for hr pts (Table). **Conclusions:** We examined treatment during the BCG shortage. BCG IDX and MTX were low among hrNMIBC pts. Clinical outcomes during the shortage highlight the potential to improve outcomes, especially for hr pts, and the need for alternative treatment strategies. Research Sponsor: AstraZeneca.

KM percent survival (95% CI) of rwmPFS¹, rwCFS², and rwOS³ by risk category.

Follow up Month	rwmPFS		rwCFS		rwOS	
	Non-Hr	Hr	Non-Hr	Hr	Non-Hr	Hr
12	97 (96, 98)	90 (89, 92)	97 (95, 98)	91 (90, 92)	90 (78, 100)	72 (69, 75)
24	92 (90, 94)	85 (83, 86)	92 (90, 94)	85 (83, 86)	85 (70, 100)	64 (60, 68)
36	89 (86, 91)	79 (77, 80)	89 (86, 91)	78 (76, 80)	85 (70, 100)	57 (53, 62)
48	87 (84, 90)	75 (73, 77)	87 (84, 90)	74 (72, 76)	75 (56, 100)	53 (48, 58)
60	81 (77, 85)	70 (68, 73)	81 (77, 85)	70 (67, 73)	– (–, –)	47 (42, 53)

¹Real-world modified progression free survival.

²Real-world cystectomy-free survival.

³Real-world overall survival.

Neoadjuvant and adjuvant (neoadj-adj) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants with cisplatin-ineligible muscle-invasive bladder cancer (MIBC): An analysis of clinically relevant subgroups in KEYNOTE-905.

Nabil Adra, Christof Vulsteke, Yohann Loriot, Alejo Rodriguez-Vida, Zhentao Zhang, Ja Hyeon Ku, Judit Olah, Anna Kolodziej, Maksym Sabadash, Gunhild Von Amsberg, Nimira S. Alimohamed, Peter H. O'Donnell, Oleksandr Lychkovsky, Girish S. Kulkarni, Jasmine Lichfield, Changting Meng, David Huang, Chethan Ramamurthy, Blanca Homet Moreno, Pongwut Danchaivijitr; Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN; Integrated Cancer Center Ghent, AZ Maria Middelares, Ghent; and Center for Oncological Research (CORE), Antwerp University, Antwerp, Belgium; Institut Gustave Roussy, Université Paris-Saclay, Villejuif, France; Hospital del Mar, Barcelona, Spain; Parkview Cancer Institute, Fort Wayne, IN; Seoul National University Hospital, Seoul, South Korea; SZTE Szent-Gyorgyi Albert Klinikai Kozpont, Szeged, Hungary; Wrocław Medical University, University Hospital named after Jan Mikulicz-Radecki, Wrocław, Poland; Lviv State Regional Oncological Center, Lviv, Ukraine; University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Arthur JE Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB, Canada; University of Chicago, Chicago, IL; MNPE Lviv Regional Clinical Hospital of Lviv Regional Council, Lviv, Ukraine; Princess Margaret Cancer Centre, Toronto, ON, Canada; Astellas Pharma Europe Ltd, Addlestone, United Kingdom; Pfizer, Bothell, WA; Merck & Co., Inc., Rahway, NJ; Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Results from the phase 3 KEYNOTE-905/EV-303 study (NCT03924895) showed that neoadj-adj EV + pembro and radical cystectomy with pelvic lymph node dissection (RC + PLND) led to superior event-free survival (EFS; HR 0.40; 95% CI 0.28-0.57), overall survival (OS; HR 0.50; 95% CI 0.33-0.74), and pathological complete response (pCR) rate (57.1% vs 8.6%) vs RC + PLND alone in participants (pts) with MIBC who were ineligible for or declined cisplatin. We report efficacy in subgroups of clinical interest, including advanced age, ECOG PS, cisplatin eligibility status, and baseline clinical tumor stage. **Methods:** Adults with stage T2-T4aNoMo or T1-T4aN1Mo MIBC by central review who were cisplatin-ineligible or declined cisplatin were randomly assigned 1:1 to neoadj-adj EV + pembro and RC + PLND vs RC + PLND alone (control). EFS by BICR, OS, and pCR (pToNo) rate by central review were analyzed in subgroups by age (≥ 65 to < 75 vs ≥ 75 yr), ECOG PS (0-1 vs 2), cisplatin-ineligibility status (ineligible vs declined), and clinical stage (T2No vs T3-T4aNo vs T1-4aN1). The analyses were exploratory; no formal statistical testing was performed. **Results:** 170 pts were assigned to EV + pembro and 174 to control. Median follow-up at data cutoff (Jun 6, 2025) was 25.6 mo (range 11.8-53.7). 30 pts in the EV + pembro arm and 32 in the control arm had stage T2No MIBC; 133 and 132 pts had stage T3-T4aNo; 7 and 10 had stage T1-4aN1. In pts with T2No MIBC, median EFS was not reached (NR) with EV + pembro vs NR with control (HR 0.26; 95% CI 0.08-0.80), and pCR rate was 60.0% vs 18.8%. In pts with T3-T4aNo MIBC, median EFS was NR with EV + pembro vs 17.2 mo with control (HR 0.43; 95% CI 0.29-0.63); median OS was NR vs 41.7 mo (HR 0.54; 95% CI 0.35-0.82); pCR rate was 57.1% vs 6.8%. In pts with T1-4aN1 MIBC, median EFS was 36.7 vs 7.2 mo (HR 0.35; 95% CI 0.09-1.40); pCR rate was 42.9% vs 0%. OS for T2No and T1-4aN1 will be assessed after additional follow-up (currently < 10 events). Outcomes by age, ECOG PS, and cisplatin eligibility are shown in the Table. **Conclusions:** An efficacy benefit was observed with neoadj-adj EV + pembro added to RC + PLND vs RC + PLND alone across clinically relevant subgroups, consistent with the ITT population. Results further support EV + pembro as a potential new standard treatment for pts with cisplatin-ineligible MIBC. Clinical trial information: NCT03924895. Research Sponsor: The study was conducted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in collaboration with Astellas Pharma Inc., Northbrook, IL, USA, and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	Age ≥ 65 to < 75 yr EV+P		Age ≥ 75 yr EV+P		ECOG 0-1 EV+P		ECOG 2 EV+P		Cisplatin- ineligible EV+P	
	N	C	N	C	N	C	N	C	N	C
EFS, median, mo	63	77	78	68	149	148	21	26	142	139
EFS HR	NR	13.1	NR	18.8	NR	17.2	NR	9.3	NR	14.2
(95% CI)	0.41		0.50		0.44		0.19		0.37	
	(0.24-0.70)		(0.30-0.84)		(0.30-0.64)		(0.07-0.52)		(0.26-0.54)	
OS, median, mo	NR	41.7	NR	37.4	NR	42.6	NR	19.2	NR	37.4
OS HR	0.49		0.63		0.59		0.17		0.46	
(95% CI)	(0.26-0.94)		(0.36-1.10)		(0.39-0.90)		(0.05-0.59)		(0.30-0.70)	
pCR rate, %	54.0	9.1	53.8	7.4	53.7	8.8	81.0	7.7	54.9	8.6

C, control; EV+P, EV + pembro.

Neoadjuvant and adjuvant enfortumab vedotin plus pembrolizumab for participants with muscle-invasive bladder cancer who are eligible for cisplatin: Randomized, open-label, phase 3 KEYNOTE-B15 study.

Christopher J. Hoimes, Matthew D. Galsky, Begonia P. Valderrama, Marco Maruzzo, Albert Font, Tudor-Eliade Ciuleanu, Jonathan Alexander Chatzkel, Takuya Koie, Javier Puente, Yousef Zakharia, Eli Rosenbaum, Katharina Boehm, Yohann Lorient, Jens Bedke, Heidi Wirtz, Mike Mihm, Qinlei Huang, Aljosja Rogiers, Blanca Homet Moreno, Alfonso Gomez De Liaño Lista; Duke University Medical Center, Durham, NC; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Hospital Universitario Virgen del Rocío, Sevilla, Spain; Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy; Catalan Institute of Oncology, Badalona, Barcelona, Spain; Institutul Oncologic Prof Dr Ion Chiricuță and University of Medicine and Pharmacy Iuliu Hațieganu, Cluj-Napoca, Romania; Department of Medicine, Division of Hematology/Oncology, University of Florida; and Moffitt Cancer Center and Research Institute, Gainesville, FL; Gifu University Hospital, Gifu City, Japan; Hospital Universitario Clínico San Carlos, Medical Oncology Department, Madrid, Spain; Division of Hematology and Medical Oncology, Mayo Clinic Arizona, Phoenix, AZ; Rabin Medical Center, Petah Tikva, Israel; Universitaetsklinikum Carl Gustav Carus, Dresden, Germany; Institut Gustave Roussy, Université Paris-Saclay, Villejuif, France; Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Germany; Pfizer Inc., Bothell, WA; Astellas Pharma Inc., Northbrook, IL; Merck & Co., Inc., Rahway, NJ; Medical Oncology Department - Complejo Hospitalario Universitario Insular-Materno Infantil, Universidad de Las Palmas de Gran Canaria, Las Palmas De Gran Canaria, Spain

Background: Enfortumab vedotin (EV) + pembrolizumab (pembro) is the established first-line standard of care for locally advanced/metastatic urothelial carcinoma and represents a novel neoadjuvant and adjuvant treatment strategy for patients with muscle-invasive bladder cancer (MIBC) who are ineligible for cisplatin-based chemotherapy. The randomized phase 3 KEYNOTE-B15/EV-304 study (NCT04700124) evaluates neoadjuvant EV + pembro followed by radical cystectomy plus pelvic lymph node dissection (RC + PLND) and adjuvant EV + pembro vs neoadjuvant chemotherapy followed by RC + PLND in participants (pts) with MIBC who are eligible for cisplatin-based therapy. **Methods:** Pts with clinical stage T2–T4aNoMo or T1–T4aN1Mo MIBC (confirmed by central pathology and central imaging assessment) who were eligible for cisplatin-based chemotherapy and RC + PLND were randomized 1:1 to receive either 4 cycles neoadjuvant EV 1.25 mg/kg IV on days 1 and 8 + pembro 200 mg IV on day 1 Q3W, followed by RC + PLND, and adjuvant 5 cycles EV + 13 cycles pembro (EV + pembro arm) vs 4 cycles neoadjuvant gemcitabine 1000 mg/m² on days 1 and 8 + cisplatin 70 mg/m² on day 1 Q3W, followed by RC + PLND (cis + gem arm). The primary endpoint was event-free survival (EFS) by blinded independent central review. Key secondary endpoints were pathological complete response (pCR) rate by blinded central pathological review and overall survival (OS). Safety was a secondary endpoint; AEs of special interest were based on distinct prespecified lists for each drug. **Results:** A total of 405 and 403 pts were randomized to EV + pembro and cis + gem, respectively. Median time from randomization to the data cutoff date of October 27, 2025 was 33.6 months (range, 22.5–53.6). Baseline characteristics were generally balanced between groups. EV + pembro significantly improved EFS (median NR vs 48.5 mo; 24-mo estimated EFS rate 79.4% vs 66.2%; HR 0.53, 95% CI 0.41–0.70; 1-sided $P < .0001$), OS (median NR vs NR; 24-mo estimated OS rate 86.9% vs 81.3%; HR 0.65, 95% CI 0.48–0.89; 1-sided $P = .0029$), and pCR rate (55.8% vs 32.5%; estimated difference 23.4%, 95% CI 16.7–29.8; 1-sided $P < .0001$) vs cis + gem. Grade ≥ 3 treatment-emergent AEs occurred in 75.7% of pts with EV + pembro and 67.2% with cis + gem. Most common grade ≥ 3 drug-related AE of special interest for EV was skin reactions (14.1%); most common grade ≥ 3 AE of special interest for pembro was severe skin reactions (13.9%). **Conclusions:** Neoadjuvant and adjuvant EV + pembro significantly improved EFS, OS, and pCR rate compared with neoadjuvant gem + cis in pts with MIBC who were eligible for cisplatin-based chemotherapy. The safety profile of EV + pembro was consistent with prior experience with the combination. These results support EV + pembro as an effective perioperative treatment option in this setting. Clinical trial information: NCT04700124. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Astellas Pharma Inc., Northbrook, IL, USA and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in Dec. 2023.

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

Junru Chen, Haoyang Liu, Qiyu Zhu, Chenhao Xu, Qiang Wei, Yige Bao, Peng Zhang, Kaijie Wu, Zhenhua Liu, Pengfei Shen, Hao Zeng; Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China; West China Hospital, Sichuan University, Chengdu, China; Department of Urology, West China Hospital, Sichuan University, Chengdu, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; Department of Urology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: Disitamab vedotin (DV), a HER2-targeted antibody–drug conjugate (ADC), has shown efficacy in metastatic urothelial carcinoma. However, its role in high-risk non-muscle-invasive bladder cancer (HR-NMIBC) patients with HER2 overexpression remains unexplored. We report preliminary findings from an ongoing phase II trial evaluating DV as adjuvant or rescue therapy in this population. **Methods:** Two cohorts were enrolled: patients receiving adjuvant therapy following transurethral resection (cohort A) and those undergoing rescue therapy after BCG failure (cohort B). Eligible patients had HR-NMIBC with HER2 overexpression. DV was administered at 120 mg intravenously every 2 weeks for up to 10 cycles. The primary endpoints were safety, 12-month recurrence-free survival (RFS) in cohort A, and 3-month clinical complete response (cCR) rate in cohort B. Secondary endpoints included 6-month RFS (cohort A) and duration of response (DOR, cohort B). Exploratory analyses evaluated the prognostic value of urinary tumor DNA (utDNA) using samples collected at baseline, end of treatment, and at the time of disease recurrence. This study is registered with ClinicalTrials.gov (NCT05996952). **Results:** Between September 2023 and October 2025, 28 patients were enrolled—22 in cohort A (median age 62 years [range, 33–75]; 3 women [13.6%]) and 6 in cohort B (median age 66 years [range, 60–72]; all men). Median follow-up was 13.4 months (range, 2.1–24.2) for cohort A and 17.0 months (range, 1.8–22.9) for cohort B. In cohort A, 6- and 12-month RFS rates were 95.2% and 73.4%, respectively. In cohort B, the 3-month cCR rate was 100%, and the median DOR was not reached (range, 1.7–19.7 months). All patients experienced treatment-related adverse events (TRAEs); 4 patients (14.3%) had grade ≥ 3 TRAEs. The most common TRAEs were elevated alanine aminotransferase (42.9%), alopecia (42.9%), and fatigue (35.7%). Exploratory analysis of baseline utDNA status demonstrated significant prognostic stratification, with positive patients exhibiting inferior 1-year RFS compared to those with negative status (50% vs. 91%, $P=0.043$). **Conclusions:** DV demonstrated a manageable safety profile and encouraging efficacy in patients with HR-NMIBC and HER2 overexpression in both adjuvant and rescue settings. The trial is ongoing, following a Simon two-stage optimal design, with a target enrollment of 52 patients in cohort A and 25 in cohort B. Study initiation was in May 2023. Clinical trial information: NCT05996952. Research Sponsor: None.

Molecular characterization of residual disease post-neoadjuvant sacituzumab govitecan (SG), pembrolizumab, or their combination in patients with muscle-invasive bladder cancer (MIBC).

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

Background: In patients (pts) with MIBC, we tested the activity of neoadjuvant SG (SURE-01, NCT05226117), SG + pembrolizumab (SURE-02, NCT0535218) and pembrolizumab alone (PURE-01, NCT02736266), followed by surgery. We aimed to molecularly characterize the residual post-neoadjuvant therapy (NAT) MIBC and its changes from baseline samples. **Methods:** Post-NAT samples (ypT $\geq$ 2) were available for transcriptome analyses from 12 pts in SURE-01, 24 in SURE-02, and 26 post-pembrolizumab alone. Decipher bladder genomic subtyping classifier (GSC) expression profiling assay (Veracyte) was used to compare molecular subtyping distributions and genes/signatures expressions between matched pre-post NAT samples, including 192 locked transcriptomic signatures in GRID (v3.1) and pre-specified therapeutic target genes. FGFR3-active tumors were determined using a previously-developed long non-coding RNA (lncRNA)-based classifier. The clinical primary endpoint was event-free survival (EFS). **Results:** Post-NAT molecular subtyping identified Luminal (L) vs non-Luminal (NL) tumors in: 17% (2/12) vs 83% (10/12) (SURE-01), 21% (5/24) versus 79% (19/24) (SURE-02), and 8% (2/26) versus 92% (24/26) (PURE-01). In total, 21 pts from SURE studies and 22 from PURE-01 had matched pre-post NAT samples. Consensus molecular subtyping revealed a concordance in 86% (6/7) of pts in SURE-01, 57% (8/14) in SURE-02 and 36% (8/22) in PURE-01. Stroma-rich tumors were found in 17% (2/12), 29% (7/24) and 50% (13/26) of post-NAT samples. After NAT, we found a decrease in L subtypes in SURE-01 (57% $\rightarrow$ 29%) and in SURE-02 (36% $\rightarrow$ 14%) vs an increase in stroma-rich (Consensus) subtype in SURE-02 (7% $\rightarrow$ 36%) and in PURE-01 (14% $\rightarrow$ 50%). Elevation of TGF- β signaling hallmark (p=0.02) and immune exclusion (p=0.02) scores characterized post-NAT samples in SURE-01, while in SURE-02 we found elevated stromal gene scores (p=0.004) and lower DNA repair hallmark scores (p=0.03) after NAT. Comparing matched samples from SURE-01 and 02, we found significantly decreased TROP2 expression scores (p=0.03) and lower HER2 (p=0.06) and NECTIN4 expression (p=0.07). Application of the lncRNA-based FGFR3-activity classifier revealed a total of 10/36 (28%) FGFR3-active tumors post-NAT in SURE-01 and SURE-02, all without EFS events during follow-up. For SURE-02, we found 4/24 (17%) pts harboring claudin-low tumors post-NAT, who did not experience EFS events following adjuvant pembrolizumab, similar to the low EFS rate observed in PURE-01 (N=7, 22%). **Conclusions:** This study expands our knowledge on residual MIBC after various NAT, displaying a noteworthy plasticity and significant changes post-NAT that are important to unveil the biology of these tumors and putative biomarkers for sequential therapies. Research Sponsor: AIRC (Associazione Italiana per la Ricerca e la Cura del Cancro); IG 2022 ID 27746.

TRUCE-11: An open-label, single-arm, multicenter phase II study of tislelizumab combined with nab-paclitaxel for muscle-invasive urothelial bladder carcinoma.

Zhouliang Wu, Yunkai Qie, Chong Shen, Peng Li, Ning Kang, Kaixuan Du, Hailong Hu; The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Neoadjuvant tislelizumab plus nab-paclitaxel may enhance pathologic response in muscle-invasive bladder cancer (MIBC), and TRUCE-11 evaluates its efficacy and safety prior to radical cystectomy (RC). **Methods:** TRUCE-11 is a multicenter phase II neoadjuvant study for eligible MIBC pts who had pure or mixed urothelial carcinoma of the bladder (cT2–4aNxMo). Pts received nab-paclitaxel 125 mg/m² IV on day 1, followed 2 h later by tislelizumab 200 mg IV (Q3W) for 2–3 cycles, then underwent RC with pathologic assessment. Imaging and urine cytology were performed at baseline and post-treatment. The primary endpoint was pathologic complete response (pCR). Secondary endpoints included pathologic downstaging rate (PaIR, $\leq$ pT1), adverse events (AEs), and overall survival (OS). Exploratory analyses evaluated radiomics features (bladder MRI, PET/CT, and contrast-enhanced ultrasound) and serum biomarkers, including peripheral blood tumor whole-genome chromosomal aberration assay (PB-TWGCA). Transcriptomic biomarker discovery further highlighted GRHL1 using bulk RNA-seq and paired baseline/RC tumor scRNA-seq. **Results:** Between March 2024 and January 2026, 27 pts were enrolled; 21 underwent RC after neoadjuvant therapy. Among RC pts (n=21), 11 pts achieved pCR (52%) and 13 achieved PaIR ($\leq$ pT1, 62%). The most common grade 1–2 AEs were alopecia (86%), fatigue (76%), rash (43%), decreased appetite (38%), and fever (14%). No grade 3–4 AEs (CTCAE) were observed. After a median follow-up of 247 days (range, 65–677), all pts were alive. Among pts achieving pCR, pre-cystectomy MRI (DWI/ADC) showed no residual diffusion restriction and/or PET/CT showed no malignant findings, concordant with pathology. In 6 pCR pts with contrast-enhanced ultrasound, 5 (83%) demonstrated marked reduction or disappearance of tumor hypervascularity during treatment. In 5 pts, PB-TWGCA r-score was consistent with tumor burden. Transcriptomic analyses further suggested that tumor-cell GRHL1 expression might be underlying markers that predict adverse outcomes for the pCR and non-pCR pts cohorts in this crew. **Conclusions:** Neoadjuvant tislelizumab plus nab-paclitaxel achieved a high pCR and downstaging rate with no grade 3–4 AEs in pts with MIBC undergoing RC. Multimodal imaging and circulating/transcriptomic biomarkers (PB-TWGCA r-score and tumor-cell GRHL1) may aid response evaluation and require confirmation in larger cohorts. Clinical trial information: NCT05328336. Research Sponsor: Scientific Research Project of Tianjin Municipal Education Commission; grant no. 2024KJ192.

Neoadjuvant sacituzumab govitecan in patients with muscle-invasive bladder cancer: Final results and biomarker analyses of the SURE-01 trial.

Brigida Anna Maiorano, Joep de Jong, Antonio Cigliola, Chiara Mercinelli, James A. Proudfoot, Giuseppe Basile, Valentina Tateo, Michela Piacentini, Enrico Tomasi, Elai Davicioni, Marco Moschini, Giorgio Brembilla, Maurizio Colecchia, Francesco De Cobelli, Jeffrey S. Ross, Russell William Madison, Candice Francheska Tambaoan, Alberto Briganti, Francesco Montorsi, Andrea Necchi; Department of Medical Oncology, IRCCS San Raffaele Hospital, Milano, Italy; Erasmus University Medical Center, Rotterdam, Netherlands; IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; Department of Medical Oncology, IRCCS San Raffaele Hospital, Comprehensive Cancer Center and Vita-Salute San Raffaele University, Milan, Italy; Veracyte, Inc., South San Francisco, CA; Urology Unit, IRCCS San Raffaele Milano, Milan, Italy; Department of Medical Oncology, IRCCS San Raffaele Hospital, Comprehensive Cancer Center, Milan, Italy; Pharmacy Unit, IRCCS San Raffaele Hospital, Comprehensive Cancer Center, Milan, Italy; Decipher Biosciences, 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, Fondazione IRCCS Istituto Nazionale Tumori di Milano, Milan, Italy; Foundation Medicine, Inc., Cambridge, MA; Foundation Medicine, Inc., Boston, MA; 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, Comprehensive Cancer Center; Vita-Salute San Raffaele University, Milan, Italy

Background: To evaluate neoadjuvant sacituzumab govitecan (SG), followed by radical cystectomy (RC), in patients with muscle-invasive bladder cancer (MIBC) who are ineligible for/refuse neoadjuvant chemotherapy (NAC). We report the results of the primary analysis and final biomarker analyses of the open-label, phase 2 SURE-01 trial (NCT05226117). **Methods:** Patients aged ≥ 18 years, ECOG PS 0-1, with histologically confirmed cT2-T4aN0M0 MIBC, ineligible/refusing NAC, and scheduled for RC received 4 cycles of SG 10 mg/Kg on D1 and D8, every three weeks (Q3W), followed by RC. The primary outcome measure was the pathological complete response (pCR) rate. Transcriptome-wide analyses and comprehensive genomic profiling assays were performed on baseline tumor samples. **Results:** From 03/22 to 07/25, 44 patients were treated and efficacy evaluable. After the initial 8 patients enrolled, the protocol was amended with a SG dose of 7.5 mg/Kg, with primary prophylaxis for neutropenia, due to the occurrence of two deaths (one treatment-related). Subsequent Grade 3-4 treatment-related adverse-events (TRAE) occurred in 5 pts (13.9%). Twenty-six patients (59.1%) had a cT3-4 stage, 20 (45.5%) had a variant histology. Fourteen patients (31.8%) refused to undergo RC and underwent a repeated transurethral resection of the bladder tumor. The median follow-up was 22 months (interquartile range: 15-26). In the intention-to-treat population: the ypT0N0-x rate was 29.5% (95% confidence interval [CI]: 16.7-45.2). We observed an enrichment of ypT0 responses in non-Luminal subtypes (46% vs 14% of Luminal), with the Infiltrated Luminal subtype having the highest proportion of ypT0 (62%). Variance by subtype revealed that TOP1 had the lowest scores in the Infiltrated Luminal subtype. A few signatures involving metabolism and tumor microenvironment were statistically significantly associated with a lower odds ratio of ypT0, whereas TROP2 expression ($p=0.72$) was not. The 24-month event-free survival (EFS) rate was 71.4% (95%CI: 58-87.8) and the 24-month overall survival (OS) rate was 80.2% (95% CI: 67.7-95). Longer EFS was observed for participants with lower TOP1-expressing tumors ($p=0.04$). **Conclusions:** To our knowledge, SURE-01 is the first to report results of an antibody-drug conjugate monotherapy targeting TROP2 in the neoadjuvant setting for patients with MIBC. Neoadjuvant SG at the reduced dose of 7.5mg/kg demonstrated compelling activity and survival estimates, with a manageable safety profile, corroborating TROP2 as a suitable target for MIBC. Molecular biomarkers pointing to the payload were associated with neoadjuvant SG activity. Clinical trial information: NCT05226117. Research Sponsor: None.

Association of GLP-1 receptor agonist therapy with BCG response in high-risk non-muscle invasive bladder cancer.

Benyamin Yaniv, Chinmay Trivedi, Kriti Mittal; UMass Chan Medical School, Worcester, MA

Background: Observational studies suggest glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reduced cancer incidence and improved survival in patients with established malignancies. Cohort data in lung cancer also suggest improved outcomes with immune checkpoint inhibitor therapy among patients receiving GLP-1RAs, raising the possibility of enhanced anti-tumor immunity. Intravesical Bacillus Calmette–Guérin (BCG) remains the mainstay treatment for high-risk (HR) non-muscle invasive bladder cancer (NMIBC). We hypothesized that GLP-1RA exposure during BCG therapy is associated with more favorable clinical outcomes in HR-NMIBC. **Methods:** Patients with HR- NMIBC treated between November 1st 2015 to November 1st 2025 were evaluated retrospectively using the TriNetX US Research Network. Patients were stratified by GLP-1RA exposure before BCG initiation (with or without overlap during BCG) versus no exposure. Cohorts were propensity score-matched for demographics and comorbidities, and outcomes were evaluated using multivariable logistic regression. The primary outcome was mortality; secondary outcomes included recurrence, progression to muscle-invasive bladder cancer (MIBC), cystectomy, and distant metastasis. **Results:** A total of 12,423 patients were evaluated, of which 791 (7%) received GLP-1RAs, while 11,630 (93%) did not. After propensity score matching, 787 patients were analyzed in each group. The average age in both cohorts was 73 years. Majority of patients were white (85%), male (80%), and non-Hispanic (85%). The distribution of GLP-1RAs use included semaglutide (67%), dulaglutide (37%), tirzepatide (21%), liraglutide (17%), exenatide (8%), and lixisenatide (1%). Patients who received GLP-1RAs demonstrated a significant reduction in 10-year mortality (RR 0.65; 95% CI 0.45 – 0.93, $p = 0.017$) and a lower risk of developing MIBC (RR 0.43; 95% CI 0.26 – 0.89; $p = 0.018$). No significant changes were noted in the risk of disease recurrence, radical cystectomy or distant metastasis (Table 1). **Conclusions:** In this real-world, retrospective, multi-cohort analysis we found that patients who received GLP-1RAs prior to BCG treatment are at a decreased risk of all-cause mortality, and less likely to develop progression to MIBC. This study underscores the need for further evaluation of GLP-1RAs in patients with NMIBC treated with BCG. Research Sponsor: None.

Outcomes comparing HR-NMIBC patients exposed to GLP-1RA prior to BCG therapy versus those without exposure.

Outcome	Risk Ratio (95% CI)	<i>p</i> -value
Mortality	0.65 (0.45 – 0.93)	0.017
MIBC progression	0.43 (0.26 – 0.89)	0.018
NMIBC recurrence	0.98 (0.89 – 1.09)	0.84
Radical cystectomy	0.94 (0.72 – 1.22)	0.65
Distant metastasis	0.83 (0.62 – 1.11)	0.19

Rethinking the role of tumor size in bladder preservation: Comparing survival outcomes of radical cystectomy (RC) and tri-modality therapy (TMT).

Dawood Hasan Syed, Haritha Gandicheruvu, Jennifer Kate Beckerman, Atulya Aman Khosla, Anisha Agarwal, Gabriel Valagni, Mohammad Arfat Ganiyani, Maneesh Jain, Michael Joseph Whalen, Neil Mendhiratta, Rohan Garje, Karan Jatwani; Geisinger Health System, Wilkes-Barre, PA; Sinai Hospital/George Washington University, Baltimore, MD; George Washington University Hospital, Washington, DC; Department of Internal Medicine, William Beaumont University Hospital, Royal Oak, MI; Ascension Saint Joseph Hospital, Chicago, IL; Saint Joseph Hospital, Chicago, IL; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; The Edward P. Evans Foundation Precision Oncology Center of Excellence, Washington DC VA Medical Center, Washington, DC; George Washington University School of Medicine and Health Sciences, Washington, DC; Miami Cancer Institute, Miami, FL; George Washington University, Washington, DC

Background: TMT (maximal TURBT followed by chemoradiation) is typically reserved for bladder cancer (BC) patients with solitary tumors less than 6 cm, no extensive carcinoma in situ, and no or unilateral hydronephrosis. The National Comprehensive Cancer Network (NCCN) guidelines specify that optimal candidates for bladder preservation with chemoradiotherapy have tumors less than 6 cm; larger tumors are less likely to be completely resected and have poorer local control and survival outcomes with bladder-sparing approaches. We aimed to analyze outcomes of BC patients receiving multimodal therapy and further categorizing outcomes of RC versus TMT based on tumor sizes. **Methods:** We analyzed patients with T1–T4, N0–N3, Mo urothelial carcinoma of the bladder using the NCDB (2010–2022). Patients were grouped as: RC, neoadjuvant chemotherapy (NAC) plus RC, RC followed by adjuvant chemotherapy (AC), and TMT. Overall survival (OS) was estimated with Kaplan–Meier methods and multivariable Cox regression adjusted for common confounders for these four groups. We also further analyzed the role of tumor size for patients who received either RC or TMT. Tumor size was divided in three groups; less than 3cm, 3 to 6cm, and more than 6cm. **Results:** Among 33,836 patients (median age 68y), treatment groups were as follows: RC alone (34%), NAC–RC (23%), RC–AC (21%) and TMT (22%). BC specific prognostic factors like tumor size more than 6cm vs 3cm (HR 1.70 (1.62–1.77) ($p < 0.001$)) and lymphovascular invasion (LVI) (HR 1.94 (1.87–2.00), $p < 0.001$)) were independently associated with poor OS. In our analysis, NAC–RC (HR 0.67 (0.64–0.70), $p = 0.001$) followed by RC–AC (HR 0.72 (0.69–0.75), $p = 0.001$) conferred the heaviest OS benefit. When tumor size was investigated as a prognostic factor comparing RC versus TMT, multivariate analysis showed that for both tumors less than 3cm (HR = 1.27 (1.16–1.39), $p = 0.001$) and 3cm to 6cm (HR 1.08(1.03–1.14), $p = 0.003$), RC was significantly superior in terms of OS. Interestingly, for tumors more than 6cm (HR = 0.97 (0.88–1.06), $p = 0.468$), the analysis revealed no significant difference in OS between RC and TMT. **Conclusions:** Despite NAC–RC offering the greatest overall survival (OS) benefit and being the standard of care, it is frequently underutilized as many patients are not candidates for chemotherapy. Consequently, bladder preservation strategies (BPS) are essential. Our analysis shows tumor size may dictate the optimal curative approach. For smaller tumors (< 3 cm and 3cm to 6cm), Radical Cystectomy (RC) is significantly superior to TMT in terms of OS. Conversely, for large tumors (> 6cm) RC provided no significant OS benefit over TMT. This suggests that the inherent aggressiveness of large lesions overrides any surgical advantage. Therefore, BPS must be strongly considered for tumors > 6cm when other TMT contraindications (e.g., hydronephrosis) are absent. Research Sponsor: None.

Exploration of biomarkers for TRUCE-01: Development of a urine-based efficacy prediction model.

Yuda Lin, Chong Shen, Houyuan Chen, Zihan Xue, Kaipeng Jia, Mingze Wang, Peihan Zhao, Yunkai Qie, Hailong Hu; The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Preliminary results from the TRUCE-01 phase II trial (NCT04730219) indicate encouraging antitumor activity and a manageable safety profile for the combination of the immune checkpoint inhibitor tislelizumab and nab-paclitaxel in patients with T2-4a No/X Mo muscle-invasive bladder cancer (MIBC) of predominant urothelial carcinoma histology. To identify patient subgroups that may derive particular benefit, we conducted a comprehensive biomarker analysis. **Methods:** We performed whole-exome sequencing (WES) on baseline tumor tissue from 44 patients. Concomitantly, urine samples were collected during treatment. Baseline urine from 44 patients was subjected to 808-panel circulating tumor DNA (ctDNA) detection, and low-depth whole-genome sequencing (WGS) was performed across three time points (pre-treatment, during treatment, and post-treatment) for 47 patients. **Results:** The classic biomarker PD-L1 expression failed to predict complete response (CR). Urine-derived biomarkers showed high concordance with tissue-based mutation profiles. Specifically, urinary mutations in RB1, ERCC2, and AR were associated with CR, while mutations in ELF3, KDM6A, and TP53 were linked to non-clinical response (NCR). Baseline ctDNA levels ($p=0.016$) and baseline ($p=0.011$)/post-treatment ($p=0.0011$) WGS scores were significantly higher in the NCR versus CR group, potentially reflecting higher tumor burden. Interestingly, only two patients who achieved CR later experienced disease progression; both showed a rising trend in WGS scores during treatment, suggesting that CR does not ensure long-term favorable prognosis and that dynamic urine monitoring may be crucial during treatment. Finally, we developed a predictive model integrating urinary WGS scores, ctDNA scores, and efficacy-associated mutation genes. This integrated model achieved an area under the curve (AUC) of 0.930, significantly outperforming models based on WGS score alone (AUC=0.695) or ctDNA score alone (AUC=0.749). **Conclusions:** Urine-based biomarker assays show promise for predicting response to chemo-immunotherapy in MIBC. Further studies with expanded sample sizes and multi-center validation are warranted to confirm these findings and assess their clinical utility in broader patient cohorts. Clinical trial information: NCT04730219. Research Sponsor: None.

Chemoablation with oral erdafitinib in recurrent *FGFR3*-altered non-muscle-invasive bladder cancer: A phase II window-of-opportunity trial.

Muhammad Hassan Alkazemi, Irina Ostrovnya, Ao Zhang, Gal Wald, Christian Hernandez, Ali Ghasemzadeh, Mark Farha, Ryan Norton, Morgan Tomberlin, Melissa McCarter, Patricia Zagajski, Kara Hildreth, Hikmat Al-Ahmadie, Alvin C. Goh, Bernard H. Bochner, Mahadi Baig, Jonathan E. Rosenberg, Gopa Iyer, Eugene J. Pietzak; Urologic Oncology Service, New York City, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Janssen Research & Development, Raritan, NJ

Background: Non-muscle invasive bladder cancer (NMIBC) frequently recurs despite intra-vesical treatments, necessitating repeated transurethral resections of bladder tumors (TURBT). *FGFR3* alterations are common in NMIBC and may be a potential therapeutic target. Erdafitinib, a pan-*FGFR* inhibitor, is approved for metastatic urothelial cancer, but its efficacy as a chemoablative agent in recurrent NMIBC is not yet established. This trial evaluates the efficacy of oral erdafitinib as a chemoablative treatment in patients with recurrent *FGFR3*-altered NMIBC. **Methods:** Patients with recurrent NMIBC and *FGFR3* alterations detected with MSK-IMPACT were given oral erdafitinib (6 mg daily) for ~28 days before TURBT. Tumor response was assessed using RECIT-Bladder criteria, and tissue, blood, and urine samples were collected for pharmacodynamic analyses and biomarker exploration. Toxicities were graded using CTCAE v5.0. **Results:** A total of 20 patients with recurrent NMIBC and confirmed *FGFR3* mutations were enrolled in the study. The most common mutations were S249C (n=12), Y373C (n=3), and R248C (n=3). Most patients (70%) had a history of low-grade Ta (LG Ta) tumors. All patients had received at least one prior intravesical therapy, with 55% having undergone multiple courses of BCG, gemcitabine, mitomycin, or combination regimens. The objective response rate (ORR) was 75% (15/20), with complete response (CR) achieved in 11 patients (55%). No grade ≥ 3 toxicities were observed. **Conclusions:** Oral erdafitinib demonstrated efficacy in reducing tumor burden in select *FGFR3*-altered NMIBC in this window-of-opportunity trial. Clinical trial information: NCT04917809. Research Sponsor: Janssen; ASCO YIA.

Durvalumab (D) in combination with BCG induction and maintenance (I + M) therapy for BCG-naïve, high-risk non-muscle-invasive bladder cancer (NMIBC): 5-year overall survival (OS) analysis and patient-reported outcomes (PROs) from POTOMAC.

Maria De Santis, Neal D. Shore, Hiroyuki Nishiyama, Michal Krawczyński, Artur Seyitkuliev, Felix Guerrero-Ramos, Ruslan Zukov, Takashi Kawahara, Lieven Goeman, Thomas Powles, Kilian Martin Gust, Susan Feyerabend, Manish Patel, Girish S. Kulkarni, Thierry Lebre, Hans M. Westgeest, Ana Quartilho, Aleksandra Dabrowska, Angie Marsh, Joan Palou; Department of Urology, Charité Universitätsmedizin Berlin, Berlin, Germany and Department of Urology, Medical University of Vienna, Vienna, Austria; Carolina Urologic Research Center and Genesis Care/Atlantic Urology Clinics, Myrtle Beach, SC; Department of Urology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan; Clinical Research Center Sp, Poznan, Poland; St. Petersburg Hospital of the Russian Academy of Sciences, St. Petersburg, Russian Federation; Hospital Universitario 12 de Octubre, Madrid, Spain; Krasnoyarsk State Medical University, Krasnoyarsk Regional Clinical Cancer Center, Krasnoyarsk, Russian Federation; Departments of Urology and Renal Transplantation, Yokohama City University Medical Center, Yokohama, Japan; Department of Development and Regeneration, University Hospitals Leuven, Leuven, Belgium; Barts Cancer Institute, Biomedical Research Centre, London, United Kingdom; Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; Studienpraxis Urologie, Medius Klinik Nürtingen, Nürtingen, Germany; Speciality of Surgery, Westmead Hospital, Faculty of Medicine and Health, Sydney, NSW, Australia; Cancer Clinical Research Unit (CCU), Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada; Department of Urology, Suresnes, France; Amphibia Hospital, Breda, Netherlands; AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Warsaw, Poland; AstraZeneca, Mississauga, ON, Canada; Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain

Background: In the Phase 3 POTOMAC study (NCT03528694), 1 year of D in combination with BCG (I + M) resulted in a statistically significant and clinically meaningful improvement in disease-free survival vs BCG (I + M) alone, with a manageable safety profile, in patients (pts) with BCG-naïve, high-risk NMIBC. We report a planned updated 5-year OS analysis and PROs. **Methods:** Eligible pts were randomized 1:1:1 to D + BCG (I + M), D + BCG (I only), or BCG (I + M). Secondary endpoints included 5-year OS and PROs, evaluated every 8 weeks by EORTC QLQ-C30 and every 4 weeks by EORTC QLQ-NMIBC24 and PRO-CTCAE. Prespecified priority subscales were global health status/quality of life (GHS/QoL), physical functioning, and fatigue for QLQ-C30; and urinary symptoms, intravesical treatment (tx) issues, future perspective/worries, and sexual functioning for QLQ-NMIBC24. Change from baseline (CFB; mixed model for repeated measures) was assessed; a ± 10 -point score was considered clinically meaningful. **Results:** At data cutoff Oct 3, 2025 (median follow-up 72 months), the OS HR was 0.81 (95% CI, 0.54–1.19) with a 5-year OS rate of 87.6% (95% CI, 83.5%–90.8%) for D + BCG (I + M) vs 86.3% (95% CI, 82.1%–89.6%) for BCG (I + M). Median OS was not reached in either arm. For PRO analyses (data cutoff Apr 3, 2025), QLQ-C30 and QLQ-NMIBC24 baseline compliance rates were $\geq 74\%$ and $\geq 79\%$, respectively, with similar baseline scores between arms. Overall, both arms showed deterioration in QLQ-C30 adjusted mean CFB scores, with suggested clinically meaningful deterioration for fatigue with D + BCG (I + M); however, the difference between arms was small (Table). Overall QLQ-NMIBC24 adjusted mean CFB scores were numerically small and similar between arms (Table). PRO-CTCAE measures were similar between arms. **Conclusions:** Addition of 1 year of D to BCG (I + M) continued to show no detriment to OS at >5.5 years of follow-up and had no major impact on PROs for pts with BCG-naïve high-risk NMIBC. Clinical trial information: NCT03528694. Research Sponsor: AstraZeneca.

Subscales	D + BCG (I + M) Adjusted mean CFB (95% CI) ^a	BCG (I + M) Adjusted mean CFB (95% CI) ^a	Estimated difference of means (95% CI)
QLQ-C30			
GHS/QoL ^b	−7.6 (−9.19, −6.07)	−4.9 (−6.46, −3.41)	−2.7 (−4.85, −0.54)
Physical functioning ^b	−5.5 (−6.76, −4.15)	−2.8 (−4.11, −1.56)	−2.6 (−4.43, −0.81)
Fatigue ^c	10.1 (8.32, 11.90)	6.1 (4.37, 7.88)	4.0 (1.50, 6.46)
QLQ-NMIBC24			
Urinary symptoms ^c	1.7 (−0.06, 3.41)	0.4 (−1.27, 2.15)	1.2 (−1.19, 3.65)
Intravesical tx issues ^c	1.5 (−0.38, 3.28)	2.7 (0.89, 4.50)	−1.2 (−3.79, 1.29)
Future perspective/worries ^c	−5.5 (−7.54, −3.39)	−3.2 (−5.29, −1.19)	−2.2 (−5.11, 0.66)
Sexual functioning ^b	2.2 (0.47, 3.91)	1.1 (−0.60, 2.80)	1.1 (−1.30, 3.48)

^aHigher scores indicate better health (GHS/functioning) or greater burden (symptoms).

^bPositive difference favors D + BCG (I + M).

^cNegative difference favors D + BCG (I + M).

Updated efficacy and safety of SHR-1501, an IL-15R α Fc superagonist, with or without Bacille Calmette Guerin (BCG) for high-risk non-muscle invasive bladder cancer (NMIBC): A phase 1/2 study.

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

Background: SHR-1501, an IL-15 agonist fusion protein composing of a humanized antibody Fc region fused with IL-15 and IL-15R α sushi domain, demonstrated promising efficacy, well tolerance, and acceptable safety in alone or in combination with BCG in patients with BCG-naïve and BCG-unresponsive high-risk NMIBC (ASCO 2025). Here, we report the updated results of this phase 1/2 study (NCT05410730). **Methods:** In the dose-escalation phase 1a and 1b parts, SHR-1501 monotherapy (200, 400, and 600 μ g) or SHR-1501 (600 μ g) in combination with BCG (120 mg) was administered to patients with high-risk NMIBC. In the phase 2 part, patients with BCG-naïve NMIBC (cohort A), BCG-unresponsive NMIBC carcinoma in situ (CIS; cohort B), and BCG-unresponsive high-grade Ta/T1 NMIBC without CIS (cohort C) were enrolled to receive SHR-1501 (600 μ g) plus BCG (120 mg). During the induction phase, all patients received weekly intravesical study treatment for 6 weeks. In the maintenance phase, instillations were administered weekly for three weeks at months 3, 6, 12, 18, and 24 following the initial induction dose. 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 Oct 31, 2025, 112 patients were enrolled (n=8 in phase 1a; n=6 in phase 1b; n=30, 25, and 43 in cohorts A, B, and C in phase 2). The median follow-up duration was 23.0 months (range 3.5–25.6) in patients with BCG-naïve NMIBC, 6.5 months (range 2.6–21.2) in patients with BCG-unresponsive NMIBC CIS, and 13.5 months (range 2.5–23.1) in patients with BCG-unresponsive high-grade Ta/T1 NMIBC without CIS. In cohort B, the overall CR rate was 80.0% (20/25), the median DFS was 12.0 months (95% CI 6.0–NR). The 12-mo DFS rate was 90.3% (95% CI, 72.8–96.8) in patients with BCG-naïve NMIBC and 62.7% (95% CI, 44.9–76.1) in patients with BCG-unresponsive high-grade Ta/T1 NMIBC without CIS. The 18-mo DFS rates were 90.3% (95% CI, 72.8–96.8) and 58.2% (95% CI, 39.6–72.9), respectively. Treatment-related adverse events (TRAEs) and grade 3 TRAEs occurred in 90 (86.5%) and 19 (18.3%) of 104 patients with SHR-1501 + BCG. The most common TRAEs were urinary tract infection (62.5%) and pollakiuria (35.6%). No TRAEs led to death. **Conclusions:** This updated analysis confirms the promising efficacy and manageable safety profile of SHR-1501 monotherapy or in combination with BCG in BCG-naïve and BCG-unresponsive high-risk NMIBC patients. Two randomized, controlled phase 3 trials are underway in both BCG-unresponsive and BCG-naïve, high-risk NMIBC populations, with the recommended dose of 600 μ g SHR-1501 plus BCG. Clinical trial information: NCT05410730. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd.

Patient-reported outcomes from IMvigor011: A phase 3 study of circulating tumor (ct)DNA–guided adjuvant atezolizumab vs placebo in muscle-invasive bladder cancer (MIBC).

Joaquim Bellmunt, Shilpa Gupta, Miguel A. Climent Duran, Fatih Köse, Karine Martins da Trindade, Naiara Sagastibelza Marinelaarena, Rosa Tambaro, Robert A. Huddart, Pablo Gajate, Alison Jane Birtle, Hongqian Guo, Tomoya Fukawa, Atsushi Komaru, Yukio Kageyama, Wataru Obara, Bo Ci, Elizabeth Steinberg, Janelle Soong, Siobhán Connor-Ahmad, Thomas Powles; Dana-Farber Cancer Institute and Harvard University, Boston, MA; Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH; Fundación Instituto Valenciano de Oncología, Valencia, Spain; Başkent University, Adana, Turkey; Instituto D'Or de Pesquisa e Ensino, Fortaleza, Brazil; University Hospital Donostia, Donostia, Spain; Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, United Kingdom; Ramón y Cajal University Hospital, Madrid, Spain; University of Manchester, Manchester, University of Lancashire and Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China; Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan; Chiba Cancer Center, Chiba, Japan; Saitama Cancer Center, Saitama, Japan; Iwate Medical University, Morioka, Japan; Genentech, Inc., South San Francisco, CA; Roche Products Limited, Welwyn Garden City, United Kingdom; Roche Products Limited, Welwyn, United Kingdom; Barts Cancer Institute, NIHR Biomedical Research Centre, Queen Mary University of London, London, United Kingdom

Background: IMvigor011 (NCT04660344) showed that serial ctDNA-based molecular residual disease (MRD) monitoring can identify patients (pts) with MIBC at very high risk of recurrence who benefit from adjuvant atezolizumab (atezo), demonstrating statistically significant and clinically meaningful improvements in DFS and OS vs placebo (pbo) in pts who tested ctDNA+. Pts who persistently tested ctDNA– had low risk of recurrence or death without adjuvant treatment (tx; Powles *NEJM* 2025). Here we report pt-reported outcomes (PROs). **Methods:** Pts with MIBC and no radiographic disease were enrolled and underwent serial ctDNA monitoring for up to 1 year after cystectomy; pts who tested ctDNA+ and remained disease-free were randomized to atezo or pbo every 4 weeks (wk) for 12 cycles or up to 1 year. PROs were assessed on Day (D)1 of Cycle (C)1, C3, C5, C7, C9, and C11, and at tx discontinuation. Time to confirmed deterioration (TTCD) analysis of physical functioning (PF), role functioning (RF), and global health status/quality of life (GHS/QoL) were secondary endpoints. Symptoms, functioning, and GHS/QoL per EORTC QLQ-C30, and tx side-effect burden per EORTC IL46, were exploratory endpoints. Relevant adverse events (AEs) were graded per NCI CTCAE v5. **Results:** Eligible pts who tested ctDNA+ (n=250) were randomized to atezo (n=167) or pbo (n=83). QLQ-C30 completion was >94% at C1D1 and >87% during tx, and >72% and >90%, respectively, for IL46. C1D1 completion rates were similar between arms. TTCD in PF, RF, and GHS/QoL showed no evidence of a difference between arms (Table). There was no clinically meaningful difference in mean change from C1D1 in symptoms, functioning, and GHS/QoL over time through C11D1 and between arms. From C1D1 to C11D1, >90% of pts reported little or no tx side-effect burden in both arms. Relevant safety data showed consistency between AEs and PROs. **Conclusions:** ctDNA-guided adjuvant atezo provided clinically meaningful DFS and OS benefit without negatively impacting pt-reported QoL. Clinical trial information: NCT04660344. Research Sponsor: F. Hoffmann–La Roche Ltd.

		Atezo (n=167)	Pbo (n=83)	Stratified HR ^a (95% CI)
QLQ-C30, median TTCD ^b (95% CI), mo	PF	25.1 (18.5, NE)	NE (19.4, NE)	1.25 (0.76, 2.07)
	RF	18.5 (12.2, NE)	NE (19.4, NE)	1.45 (0.88, 2.40)
	GHS/QoL	35.4 (19.3, NE)	16.5 (10.9, NE)	0.71 (0.45, 1.12)
IL46 tx side-effect burden, % of pts	Atezo C1D1 (n=131)	Atezo C11D1 (n=60)	Pbo C1D1 (n=60)	Pbo C11D1 (n=22)
	Not at all/a little	93.9	98.3	98.3
	Quite a bit	6.1	1.7	1.7
	Very much	0	0	0

^aStratification factors: Nodal status (+ vs –); tumor stage (≤pT2 vs pT3/4); programmed death ligand-1 status (<5% vs ≥5% of immune cells); time from cystectomy to first ctDNA+ sample (≤20 vs >20 wk).

^bTime from randomization to first clinically meaningful deterioration (≥10-point decrease) at either: ≥2 consecutive visits; or at 1 visit followed by death due to cancer progression ≤8 wk from last deteriorated PRO visit.

NE, not evaluable.

Molecular classification of neuroendocrine carcinoma of the bladder.

Shijia Li, Margaret Han, Christina Thai, Kayla Viets Layng, Lorenzo Grego, Unnati Jariwala, Jonathan Chou, Vadim S. Koshkin, Terence W. Friedlander, Claire Mulvey, Emily K. Bergsland, Rahul Raj Aggarwal, Eric J. Small, Xiaolin Zhu; Bridgeport Hospital, Bridgeport, CT; School of Medicine, University of California San Francisco, San Francisco, CA; Tempus Inc., Chicago, IL; Tempus AI, Inc., Chicago, IL; Tempus AI Inc., Chicago, IL; University of California, San Francisco, San Francisco, CA; Department of Medicine, University of California San Francisco, San Francisco, CA; University of California San Francisco, San Francisco, CA

Background: Neuroendocrine carcinoma (NEC) of the bladder is a rare and aggressive cancer with limited treatment options. Recent studies reported molecular subtypes resembling small cell lung cancer (SCLC), specifically those associated with transcription factors (TFs) ASCL1, NEUROD1, and POU2F3. A subset of bladder NEC remains unclassified. ATOH1 was recently identified as a TF associated with a minority of SCLC tumors. **Methods:** The Tempus Lens Platform (Tempus AI, Inc., Chicago, IL) was used to query the multimodal de-identified database and establish a cohort of 121 patients with bladder NEC. We analyzed the genomic and transcriptomic profiles using tempusverse and custom code. K-means consensus clustering of gene expression was used to identify molecular subtypes; subsequently, tumor genetic alterations (single-nucleotide variants [SNVs], indels, and copy number alterations [CNAs]) and gene expression profiles were compared across these subtypes. Fisher's exact test was used to compare the frequency of events across categorical groups. limma-trend and empirical Bayes statistics were used for differential gene expression analysis. The Cox proportional hazards model and the Kaplan-Meier method were used for survival analysis. consensusMIBC was used for the consensus molecular classification. **Results:** Within the cohort, 103 were classified as neuroendocrine (NE)-like using consensusMIBC and were further analyzed in this study. The median age at diagnosis was 71 years (interquartile range, 63–76), with a male predominance (77%). Using the four SCLC TFs (ASCL1, NEUROD1, POU2F3, and ATOH1; YAP1 was excluded as it was recently found to be expressed in the non-NE components of mixed bladder NECs), we identified a five-type system that classifies most samples: ASCL1+/NEUROD1- (n=37; 36%), ASCL1-/NEUROD1+ (n=23; 22%), ASCL1+/NEUROD1+ (n=16; 16%), POU2F3+ (n=23; 22%), and ATOH1+ (n=4; 4%). Each subtype was associated with a distinct gene expression profile with representative markers: ASCL1, SOX2, and DLL3 (ASCL1+/NEUROD1-); NEUROD1, NEUROD4, and SSTR2 (ASCL1-/NEUROD1+); ETV1, NKX2-1, and NKX2-2 (ASCL1+/NEUROD1+); POU2F3, GFI1B, and POU2AF2 (POU2F3+); ATOH1, POU4F3, and USH2A (ATOH1+). POU2F3+ tumors expressed low NE markers and high PLCG2 and ERBB3; ATOH1+ tumors often expressed NE markers and tended to overexpress ALK. No statistically significant tumor SNVs, indels, or CNAs were differentially observed across the subtypes; TP53 (92%), TERT (82%), and RB1 (62%) were the most frequently altered genes in the entire cohort. Univariate analysis showed a worse real-time overall survival of ASCL1+/NEUROD1+ (hazard ratio [HR]=3.1, p=0.01), POU2F3+ (HR=3.4, p=0.001), and ATOH1+ (HR=8.4, p=0.0003), compared with ASCL1-/NEUROD1- tumors. **Conclusions:** We report an effective, clinically relevant molecular classification system for bladder NECs, including the newly described ATOH1+ subtype. Research Sponsor: University of California San Francisco.

A phase II trial of neoadjuvant zanzalintinib (ZANZA) plus nivolumab (NIVO) in patients with locally advanced and/or surgically challenging clear cell renal cell carcinoma (EXPLORE-RCC).

Qian Qin, Song Zhang, Isamu Tachibana, Lin Lin, Elshad Hasanov, Eric A. Singer, Daniel M. Geynisman, Alexander Kutikov, Matthew R. Zibelman, Melissa A. Reimers, Jonathan Maldonado, David James VanderWeele, Shilajit Kundu, Asit K.R. Paul, John W. Melson, Kris Gaston, Vitaly Margulis, Jeffrey A. Cadeddu, Tian Zhang; Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; Peter O'Donnell Jr. School of Public Health, UT Southwestern, Dallas, TX; Department of Urology, UT Southwestern Medical Center, Dallas, TX; Department of Urology, UT Southwestern, Dallas, TX; Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; The Ohio State University & James Comprehensive Cancer Center, Columbus, OH; Fox Chase Cancer Center, Philadelphia, PA; Division of Oncology, Department of Internal Medicine, Washington University in St. Louis, St. Louis, MO; Washington University School of Medicine, St. Louis, MO; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; Northwestern University Feinberg School of Medicine, Chicago, IL; Virginia Commonwealth University - Massey Comprehensive Cancer Center, Richmond, VA; Division of Hematology and Oncology, Department of Internal Medicine, Simmons Comprehensive Cancer Center, UT Southwestern, Dallas, TX

Background: Immunotherapy doublet combinations (+/- vascular endothelial growth factor receptor-tyrosine kinase inhibitor [VEGFR-TKI]) are established for front-line treatment of metastatic, clear cell renal cell carcinoma (ccRCC). However, their role in the perioperative setting for locoregional ccRCC remains to be defined. We designed the EXPLORE-RCC trial to evaluate neoadjuvant ZANZA (novel, next generation VEGFR-TKI with short half-life) plus NIVO (PD-1 inhibitor) in patients with locally advanced ccRCC, where the combination has the potential to shrink the primary tumor, increase resectability, and/or allow a partial nephrectomy or minimally invasive approach. **Methods:** In this multisite, phase 2, open-label, single-arm trial coordinated by the Hoosier Cancer Research Network, subjects will receive ZANZA 60mg orally once daily plus NIVO intravenously per standard of care (SOC) dosing for 12 weeks (w), followed by restaging scans and an adaptive approach: (1) subjects who are deemed operable will undergo resection (Cohort A); (2) subjects who remain inoperable can receive up to 48w total of ZANZA plus NIVO (Cohort B1) with the option to undergo resection when deemed operable; or (3) subjects who have disease progression will stop protocol mandated therapy and receive subsequent SOC treatment (Cohort B2). The main inclusion criteria include age $\geq$ 18 years, ECOG Performance Status of 0-1, histologically confirmed ccRCC, and locally advanced (cT3/4, N0-1, with or without tumor thrombus) disease and/or deemed surgically challenging per surgeon discretion. Non-measurable metastasis per RECIST 1.1 criteria, including soft tissue metastasis with longest diameter $<$ 10mm or distant lymph nodes $<$ 15 mm in short axis are allowed. Main exclusion criteria are non-clear cell histology, measurable metastatic disease per RECIST 1.1 criteria, and prior systemic treatment for ccRCC. The primary endpoint is overall response rate (ORR) after 12w of therapy. This single arm trial is powered to detect an improvement in ORR from a historical rate of 30% to 45%, with 80% power and a 0.05 one-sided type I error. Estimating 10% drop out, 69 subjects will be enrolled. Key secondary/exploratory endpoints include efficacy outcomes (conversion to operable, disease free survival, overall survival, pathologic response), safety, surgery-related complications (including Clavien-Dindo), and biomarker correlatives. The trial is actively enrolling (ClinicalTrials.gov NCT06794229) at UT Southwestern and opening at Ohio State, Fox Chase Cancer Center, Virginia Commonwealth, Northwestern University, and Washington University in St. Louis. Clinical trial information: NCT06794229. Research Sponsor: Exelixis.

A multicenter randomized controlled clinical study of neoadjuvant combination of axitinib plus toripalimab to improve disease-free survival of patients with renal cell carcinoma.

Zhiling Zhang, Zhaohui Zhou, Yulu Peng, Xiaofeng Yang, Changwei Ji, Shimiao Zhu, Jiwei Huang, Shengjie Guo, Hui Han, Fangjian Zhou, Pei Dong; 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, 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 for Cancer Medicine, Guangzhou, China; Nanjing Drum Tower Hospital, Nanjing, China; Department of Urology, the Second Hospital of Tianjin Medical University, Tianjin, China; Department of Urology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 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; Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Urology Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cell carcinoma, accounting for 75–80% of cases worldwide and 60–85% in China. High risk ccRCC includes tumors larger than 7 cm (T2 stage) or those at advanced stages ($\geq T3$ or N1). Surgical resection is standard, but 30% may have recurrence, with a 2-year disease-free survival rate of 68%. Neoadjuvant therapy with axitinib and toripalimab may enhance antitumor immunity and improve prognosis for high risk patients. **Methods:** This is an open-label, multicenter, phase III randomized controlled study to assess whether neoadjuvant axitinib plus toripalimab improves disease-free survival (DFS) compared with surgery alone in patients with ccRCC at high risk of recurrence. The study is designed to enroll 298 patients with high risk ccRCC (T2G4 or T3–4 or N1) scheduled for nephrectomy. Patients must provide an adequate tumor tissue sample at screening for molecular and immune profiling. Patients will be randomly assigned to the control group or the neoadjuvant group at a 1:1 ratio. Both groups will undergo nephrectomy, while the neoadjuvant group will additionally receive preoperative treatment with axitinib plus toripalimab. Axitinib will be given for 3 months, 5 mg twice daily, orally. Toripalimab will be administered at 240 mg intravenously every 3 weeks for 4 cycles (one cycle every 3 weeks). Blood samples are collected before and after neoadjuvant treatment for exploratory molecular analysis. CT or MRI assessments will be conducted after 2 cycles of medication and before surgery. Radical nephrectomy (or partial nephrectomy, if applicable) will be performed within 1–28 days after completion of neoadjuvant therapy. For both groups, if postoperative pathology meets high recurrence risk criteria per Keynote-564—specifically, T2G4, T2 with sarcomatoid differentiation, T3, T4, any T stage with lymph node metastasis, or M1 with no evidence of disease—1 year of adjuvant toripalimab is recommended according to NCCN and EAU guidelines. Eligible patients must be diagnosed as ccRCC or RCC with a predominant clear cell component through histopathological examination. Clinical staging via CT or MRI must indicate T2, while biopsy pathology should show either nuclear grade 4 or sarcomatoid differentiation, or a classification of T3–4 or N1. Additional inclusion criteria include: signed informed consent, age ≥ 18 and < 80 years old, adequate organ function, ECOG of 0 or 1 point. The primary endpoint is 2-year DFS, defined as the time from randomization to disease recurrence or death from any cause. Secondary endpoints include cancer-specific survival, overall survival, objective response rate, major pathological response, and safety profile. Enrollment began in April 2023, and 112 of the planned 298 patients have been enrolled. Clinical trial information: NCT05738694. Research Sponsor: None.

Phase 3 study to assess the safety and efficacy of ^{177}Lu -girentuximab in advanced, relapsed, or recurrent ccRCC (LUTEON).

David Cade, Sumanta Kumar Pal, Andrew Mark Scott, Thea Faivre; Telix Pharmaceuticals, North Melbourne, VIC, Australia; City of Hope Comprehensive Cancer Center, Duarte, CA; Austin Health, Heidelberg, Australia; Telix Pharmaceuticals, Geneva, Switzerland

Background: A high unmet need remains for treatments that provide durable disease control while preserving quality of life in patients with advanced clear-cell renal cell carcinoma (ccRCC). Girentuximab is a monoclonal antibody targeting carbonic anhydrase IX (CAIX), which is expressed on >95% of ccRCC cells with limited expression in healthy tissues. Radio-labeling girentuximab with β emitting lutetium-177 (^{177}Lu -girentuximab) enables targeted delivery to CAIX-expressing tumor cells. Phase 1 - 2 data of ^{177}Lu -girentuximab in patients with metastatic ccRCC suggest favorable safety, tolerability, and efficacy profile.^{1,2,3} LUTEON is a Phase 3 study designed to assess safety and efficacy of ^{177}Lu -girentuximab in patients with advanced, relapsed or recurrent ccRCC. **Methods:** LUTEON is a 2-part, randomized, open-label, multicenter study to determine the optimal activity and schedule of ^{177}Lu -girentuximab (Part 1), and evaluate efficacy and safety of ^{177}Lu -girentuximab versus an approved monotherapy standard-of-care (SOC) comparator (Part 2). Eligible patients are aged ≥ 18 years, have relapsed or recurrent, locally advanced or metastatic, histologically or cytologically confirmed ccRCC, and have received 2-3 prior lines of systemic therapies (including a PD-1/PD-L1 inhibitor and a VEGF/VEGFR-targeting agent) for locally advanced or metastatic ccRCC. Patients must have CAIX-positive cancer as determined by ^{89}Zr -girentuximab PET (performed during screening). In Part 1, patients will be randomized 1:1 (≤ 20 /arm) to receive either 3 IV infusions of 1887 MBq ^{177}Lu -girentuximab every 8 weeks or 6 infusions of 1258 MBq ^{177}Lu -girentuximab every 4 weeks. Unacceptable toxicity is managed with predefined, clinically appropriate measures. In Part 2, patients will be randomized 1:1 to receive ^{177}Lu -girentuximab at the optimal regimen identified in Part 1 or an SOC comparator. In both parts, the end of treatment (EOT) visit occurs 3 ± 1 week after the last infusion or within 30 days of discontinuing treatment. After EOT, efficacy assessments occur every 8 ± 2 weeks for 6 months; patients will undergo tumor assessments according to RECIST 1.1 and will receive a contrast-enhanced CT and/or MRI of the chest, abdomen, and pelvis. In Part 2, after the first 6-month follow-up visits, patients continue follow-up every 12 ± 2 weeks for up to 24 months after the EOT visit or until progression of disease, death, or the initiation of new systemic anticancer therapies, whichever occurs first. The primary endpoints of Part 1 are incidence and severity of TEAEs, patient discontinuation due to TEAEs, and dosing delays due to TEAEs. The primary endpoint of Part 2 is progression-free survival, defined as time from randomization to first disease progression according to RECIST 1.1 or death due to any cause. This study is sponsored by Telix Pharmaceuticals. Clinical trial information: NCT07197580. Research Sponsor: Telix Pharmaceuticals.

LITESPARK-033: Phase 3 study of belzutifan plus zanzalintinib versus cabozantinib for recurrent clear cell renal cell carcinoma during or after adjuvant anti-PD-(L)1 therapy.

Cristina Suárez, Thomas Powles, Martin H. Voss, Marc-Oliver Grimm, Kelly N. Fitzgerald, Brian Simmons, Jerry Cornell, Joseph E. Burgents, Priyanka Chablani, Toni K. Choueiri; Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Barts Health Biomedical Research Centre, Queen Mary University of London ECMC, London, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Jena University Hospital, Jena, Germany; University of California, San Francisco, San Francisco, CA; Exelixis, Inc., Alameda, CA; Merck & Co., Inc., Rahway, NJ; Dana-Farber Cancer Institute, Boston, MA

Background: Adjuvant pembrolizumab is standard of care for patients with renal cell carcinoma (RCC) at increased risk for recurrence after nephrectomy. However, treatment options are needed following adjuvant anti-PD-(L)1 therapy because none of the currently available treatments for advanced RCC were evaluated in this setting. Belzutifan, a potent and selective hypoxia-inducible factor 2 α inhibitor, is approved for advanced RCC following a PD-(L)1 inhibitor and vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). Zanzalintinib is a multitargeted kinase inhibitor of VEGF receptors, MET, and the TAM family of kinases (TYRO3, AXL, and MER). VEGF-TKIs, such as cabozantinib, are approved as first-line treatment for advanced RCC and in patients who have received subsequent lines of therapy. Promising antitumor activity has been observed in phase 2 studies when combining a VEGF-TKI with belzutifan for advanced clear cell RCC. The randomized, multicenter, open-label phase 3 LITESPARK-033 study (NCT07227402) is designed to evaluate the efficacy and safety of belzutifan plus zanzalintinib versus cabozantinib in participants with advanced clear cell RCC who experienced recurrence during or after anti-PD-(L)1 adjuvant therapy. **Methods:** Eligible participants are aged ≥ 18 years with histologically confirmed, unresectable, advanced (stage IV) RCC with a clear cell component; have measurable disease per RECIST v1.1 as assessed by investigator; received adjuvant anti-PD-(L)1 therapy after nephrectomy; and experienced recurrence during or up to 24 months from the last dose of adjuvant therapy. Approximately 904 participants will be randomly assigned 1:1 to receive belzutifan 120 mg orally once daily plus zanzalintinib 60 mg orally once daily or cabozantinib 60 mg orally once daily. Treatment will continue until unacceptable toxicity or disease progression. Randomization will be stratified according to time of recurrence after adjuvant anti-PD-(L)1 therapy (≤ 6 months vs > 6 months after the last dose), International Metastatic RCC Database Consortium risk (favorable vs intermediate vs poor), and presence of sarcomatoid features (yes vs no). Primary end points are progression-free survival per RECIST v1.1 as assessed by blinded independent central review (BICR) and overall survival. Secondary end points are objective response rate and duration of response per RECIST v1.1 as assessed by BICR, and safety. The study is open and currently enrolling as of November 26, 2025. Clinical trial information: NCT07227402. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

ZAMBONI: A phase II study of zanzalintinib for metastatic clear cell renal cell carcinoma with bone metastases previously treated with immune checkpoint inhibitors.

Kelly N. Fitzgerald, Sweata Kaffle, Daniel Alvins, Li Zhang, Rohit Bose, Jonathan Chou, Arpita Desai, Ivan de Kouchkovsky, Terence W. Friedlander, Sarah Ching-Lan Hsu, Vadim S. Koshkin, Daniel H. Kwon, Edward Maldonado, Elizabeth Pan, Noah Spector Younger, Xiaolin Zhu, David Yoonsuk Oh, Rahul Raj Aggarwal, Eric J. Small; University of California, San Francisco, San Francisco, CA; Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of California San Francisco, San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA; Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, CA

Background: Bone metastases (BM) in metastatic renal cell carcinoma (mRCC) are associated with aggressive disease behavior and poor prognosis, particularly following progression on immunotherapy (IO)-based treatment regimens. Oral vascular endothelial growth factor receptor (VEGFR)-targeting tyrosine kinase inhibitors (TKIs) have demonstrated efficacy in mRCC with BM and have been shown to modulate production of osteoclastogenic factors in the tumor microenvironment. Zanzalintinib is a novel oral VEGFR-targeting TKI that has demonstrated a tolerable safety profile in phase I studies; its broad multikinase targeting profile and short half-life of 16–22 hours may enhance efficacy and tolerability compared with other VEGFR-targeting TKIs. However, the efficacy of zanzalintinib in patients with BM is unknown. **Methods:** This is a single-institution, phase II trial of zanzalintinib plus investigator-choice bone modifying agent (BMA) in patients with metastatic clear cell RCC with BM that has been previously treated with immunotherapy (IO). Eligible patients will have primarily clear cell histology, at least three BM including at least one BM not previously treated with radiation therapy (RT), and prior disease progression on 1–3 prior lines of therapy including at least one IO-based therapy administered in either the adjuvant or metastatic setting. Measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 is not required. Patients will receive zanzalintinib 60mg by mouth daily in 28-day cycles; treatment will be continued until disease progression or unacceptable toxicity occurs. Dose reduction, re-escalation, or interruption of up to 6 weeks is allowed for patients experiencing adverse events. Investigator-choice BMA may include zoledronic acid, pamidronate, ibandronate, or denosumab, will be administered at a standard dose/interval starting within 30 days of cycle 1, day 1 (C1D1), and continued until criteria for discontinuation of BMA or removal from study are met. RT and/or steroid therapy for symptomatic metastases, including BM, is allowed per investigator discretion. Patients will be radiologically evaluated starting 8 weeks after C1D1 and every 12 weeks thereafter. Adverse events will be monitored throughout the study and for 30 days following cessation of study treatment. Enrollment will continue until 20 patients evaluable for primary endpoint are enrolled, or up to a maximum of 24 patients. The primary endpoint is 12-month landmark progression-free survival and will be evaluated in patients with RECIST-measurable disease at baseline; key secondary endpoints include overall survival, rate of skeletal-related events, and rate of osteonecrosis of the jaw and will be measured in all patients. Clinical trial information: NCT07043608. Research Sponsor: Exelixis.

First-in-human study of [^{111}In] XYIMSR-01 SPECT/CT, a novel carbonic anhydrase IX small molecule in patients with metastatic clear cell renal cell carcinoma.

Yasser Ged, Steven P. Rowe, Mark Christopher Markowski, Xing Yang, Daniel Holt, Sangeeta Ray, Robert F. Dannals, Nirmish Singla, Mohamad E. Allaf, Andrei Gafita, Yong Du, Martin Pomper, Lilja B. Solnes; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; UT Southwestern Medical Center, Dallas, TX; Peking University, Beijing, China; Division of Nuclear Medicine and Molecular Imaging, The Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, MD; Johns Hopkins University, Department of Radiology, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; The James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, MD; Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD; UT Southwestern Medical Center, Department of Radiology, Dallas, TX

Background: Clear cell renal cell carcinoma (ccRCC) accounts for approximately 75% of renal cancers and is characterized by von Hippel–Lindau (VHL) inactivation and subsequent upregulation of hypoxia-inducible factor-2 α (HIF-2 α), leading to overexpression of carbonic anhydrase IX (CAIX) in over 95% of tumors. CAIX represents an attractive theranostic target for molecular imaging and radioligand therapy. XYIMSR-01 is a novel low-molecular-weight CAIX-targeted molecule engineered for rapid clearance, high tumor to background contrast, and potential same-day imaging. Preclinical studies demonstrated strong tumor uptake, favorable biodistribution, and selective retention in CAIX-expressing ccRCC xenografts, supporting clinical translation. Based on these findings, a first-in-human study of indium-111 labeled XYIMSR-01 using single photon emission computed tomography (SPECT/CT) imaging has been initiated in patients with metastatic ccRCC. **Methods:** This is an investigator-initiated, single-center, phase I study conducted at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, designed to evaluate the safety, tolerability, and feasibility of [^{111}In] XYIMSR-01 SPECT/CT imaging in patients with metastatic ccRCC. Eligible patients must have histologically confirmed ccRCC, ≥ 2 measurable metastatic lesions (size of each lesion at least ≥ 1.5 cm), treatment naïve, and have adequate organ and marrow function. Following informed consent, patients receive a single intravenous injection of 10.5 ± 1 mCi of [^{111}In] XYIMSR-01, followed by whole-body planar and regional SPECT/CT imaging at 2–4, 24 ± 1 , and 48 ± 1 hours post-injection. Blood samples are collected at multiple time points up to 48 hours to assess pharmacokinetics, clearance, and metabolic profile. Radiation dosimetry is calculated from serial imaging to estimate absorbed doses to tumor and normal organs. The primary objective is to assess the safety, tolerability, and feasibility of imaging with [^{111}In] XYIMSR-01. Secondary objectives include characterization of biodistribution, radiation dosimetry, and pharmacokinetics. Exploratory analyses will evaluate concordance between [^{111}In] XYIMSR-01 SPECT/CT with standard CT or MRI for lesion detection. The planned sample size is up to 10 patients. Successful completion of the study may support the development of future CAIX-targeted theranostic strategies in ccRCC. Clinical trial information: NCT07062549. Research Sponsor: None.

PEAK-1: A randomized, double-blind, active-control, multicenter phase 3 trial of casdatifan and cabozantinib versus placebo and cabozantinib in patients with advanced clear cell renal cell carcinoma.

Toni K. Choueiri, Sumanta Kumar Pal, Rana R. McKay, Cristina Suárez, John Haanen, Deepti Warad, Christopher Negro, Melissa Jeanne Eisen, Paul G. Foster, Thomas Powles; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA; UC San Diego Moores Cancer Center, La Jolla, CA; Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Division of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Arcus Biosciences, Hayward, CA; Arcus Biosciences, Inc., Hayward, CA; Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, United Kingdom

Background: For patients (pts) with advanced or metastatic clear cell renal cell carcinoma (ccRCC) who have relapsed post anti-PD-1/PD-L1 treatment, second line treatment options remain limited, consisting primarily of tyrosine kinase inhibitors (TKI) monotherapy. Hypoxia-inducible factor 2 alpha (HIF-2 α) inhibition represents a promising target as its mechanism of action has been clinically validated in ccRCC and is distinct from that of TKIs without overlapping toxicities. Casdatifan (cas) is an orally bioavailable, selective HIF-2 α inhibitor that has a potentially improved pharmacodynamic profile relative to other members of the therapeutic class (Ghasemi 2025). Combining cas with a TKI (cabozantinib [cabo]) that targets VEGFR, MET, and AXL may yield enhanced antitumor activity beyond the individual agents. Preliminary efficacy data from the Phase 2 ARC-20 Study demonstrated promising antitumor activity with the combination (cas + cabo; Choueiri 2025). PEAK-1 is currently the only Phase 3 that examines the efficacy and safety of a HIF-2 α inhibitor in combination with a TKI in ccRCC. **Methods:** PEAK-1 (NCT07011719) is an ongoing Phase 3, randomized, active-control, double-blind, 2-arm, global, multicenter study in adult pts with confirmed advanced or metastatic ccRCC who have experienced progression on or after anti-PD1 or anti-PD-L1 treatment. Approximately 720 pts will be enrolled and randomized 2:1 to treatment with 100 mg QD cas + 60 mg QD cabo (experimental arm) or placebo + 60 mg QD cabo (comparator arm). Crossover is not allowed. Stratification factors include by region (North America vs Western Europe vs rest of world); prior VEGFR-TKI (yes vs no); and International Metastatic RCC Database Consortium risk score (favorable vs intermediate/poor). Key eligibility requirements include adults (≥ 18 years) who have received anti-PD-1 or anti-PD-L1 treatment as part of the most recent regimen (either adjuvant monotherapy or first line in combination with anti-CTLA-4 or VEGFR-TKI), with ≤ 1 prior regimens in the metastatic setting. Pts must have a Karnofsky Performance Status score $\geq 80\%$, at least 1 target lesion measurable by computed tomography/magnetic resonance imaging per RECIST 1.1, and adequate organ and marrow function. Key exclusion criteria include prior treatment with a HIF-2 α inhibitor or cabo, receiving ongoing concomitant treatment with moderate or strong CYP3A4 inducers, and uncontrolled or poorly controlled hypertension (sustained blood pressure $>140/90$ mm Hg on ≥ 3 antihypertensives). The primary endpoint of the study is PFS BICR according to RECIST 1.1. Secondary endpoints include safety, overall survival, overall response rate, duration of response, and disease control rate. Pt reported outcomes using NFKSI-DRS will also be assessed. Enrolment is ongoing as of 1 Oct 2025. Clinical trial information: NCT07011719. Research Sponsor: Arcus Biosciences, Inc.

Phase II study of cemiplimab ± fianlimab following SBRT for oligometastatic clear-cell RCC (LAG-BOOST).

Abhirami Das, Syed Saqib Balkhi, Laxmi Alekhya Mitta, Abdul Qadar, Sara Vesely, Tyler Gunter, Michael Cookson, Kelly Lynn Stratton, Andrew G. McIntosh, Sanjay Patel, Brian Cross, Yuanquan Aaron Yang, Elshad Hasanov, Manojkumar Bupathi, Benjamin Garmez, Rana R. McKay, Jafer Raza, Adanma Ayanambakkam; Department of Internal Medicine, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Stephenson Cancer Center, University of Oklahoma Health Sciences, Oklahoma City, OK; University of Oklahoma Health Sciences Center, Oklahoma City, OK; University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK; Hudson College of Public Health, Oklahoma City, OK; Stephenson Cancer Center, Oklahoma City, OK; University of Oklahoma College of Medicine, Oklahoma City, OK; University of Oklahoma Health Sciences Center, Stephenson Cancer Center, Oklahoma City, OK; Pelotonia Institute for Immuno-Oncology and Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Rocky Mountain Cancer Centers, Littleton, CO; Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN; UC San Diego Moores Cancer Center, La Jolla, CA; University of Oklahoma- The Stephenson Cancer Center, Oklahoma City, OK

Background: Oligometastatic clear-cell renal cell carcinoma (ccRCC) is a biologically distinct, often indolent state where metastasis-directed therapy, including metastasectomy or SBRT, provides durable local control and delays systemic therapy. Randomized prospective trial evidence demonstrates a survival benefit with adjuvant programmed cell death-1 (PD-1) inhibition following surgical metastasectomy in oligometastatic ccRCC. However, the role of adjuvant PD-1 inhibition following stereotactic body radiation therapy (SBRT) has not been prospectively evaluated. SBRT induces immunogenic tumor cell death, enhances tumor antigen presentation, and promotes T-cell priming, providing a strong biologic rationale for evaluating PD-1 inhibition following SBRT. Beyond PD-1 blockade alone, lymphocyte activation gene-3 (LAG-3) is an inhibitory immune checkpoint expressed on tumor-infiltrating lymphocytes in ccRCC and contributes to T-cell exhaustion and immune evasion. Dual PD-1 and LAG-3 blockade has demonstrated promising antitumor activity with acceptable tolerability in early-phase studies, supporting investigation of strategies to enhance the efficacy of adjuvant PD-1 inhibition following SBRT in oligometastatic disease. **Methods:** LAG-BOOST is a 1:1 randomized, prospective, multicenter, investigator-initiated phase II trial. Eligible patients have histologically confirmed oligometastatic ccRCC, defined as ≤ 5 metastatic lesions by RECIST v1.1, all amenable to SBRT. Following SBRT to all visible lesions, patients are randomized to receive one year of adjuvant PD-1 inhibition (cemiplimab) alone or combined PD-1 and LAG-3 inhibition (cemiplimab and fianlimab). Treatment continues for up to one year or until disease progression, unacceptable toxicity, or withdrawal of consent. Patients must be naïve to systemic therapy for metastatic RCC; prior adjuvant therapy for non-metastatic RCC is permitted in the absence of radiographic disease progression within 12 months of treatment completion. Stratification is based on International Metastatic RCC Database Consortium (IMDC) risk and metastatic burden: (1) favorable or intermediate IMDC risk with 3 or fewer metastatic lesions and no brain metastases versus (2) poor IMDC risk or 4–5 metastatic lesions or the presence of brain metastases. The primary endpoint is 1-year progression-free survival (PFS). Secondary endpoints include safety and tolerability (treatment-related adverse events per CTCAE v5.0), objective response rate by RECIST v1.1, duration of response, disease control rate, and overall survival. As of submission, 2 of the planned 72 patients have been enrolled. The study is powered for H_0 : 65% versus H_a : 85% 1-year PFS, with $\alpha = 0.05$ and power = 0.8. ClinicalTrials.gov identifier: NCT07223541. Clinical trial information: NCT07223541. Research Sponsor: Regeneron Pharmaceuticals.

A phase I, first-in-human study to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activities of GenSci139 in patients with solid tumors.

Jinming Yu, Yuping Sun, Tongsen Zheng, Yu Fang, Xinjun Liang, Hongli Xu, Jinhua Wen, Bin Fu, Lei Jin, Siqin Wang, Shu Zhang, Xiao Liang, Xiang Li, Yujia Zhang, Yehua Xie, Fan Zhang, Zaili Weng, Ruirui Zhang, Yun Zhang; Shandong Cancer Hospital, Jinan, China; Cancer Hospital of Shandong First Medical University (Shandong Cancer Institute, Shandong Cancer Hospital), Jinan, China; Harbin Medical University Affiliated Cancer Hospital, Harbin, Heilongjiang, China; Department of Abdominal Oncology, Hubei Cancer Hospital, Wuhan, Hubei, China; Department of Medical Oncology, Hubei Cancer Hospital, Wuhan, Hubei, China; The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China; The First Affiliated Hospital of Nanchang University, Nanchang, China; Changchun GeneScience Pharmaceutical Co., Ltd., Changchun, China

Background: HER2 and EGFR are frequently co-expressed in solid tumors. Bispecific targeting of these receptors can produce synergistic enhancement in cell binding and internalization, potentially overcoming monotherapy resistance and maintaining efficacy in low antigen-expression settings. GenSci139 is a bispecific antibody-drug conjugate (ADC) directed against both EGFR and HER2, incorporating a cleavable linker to deliver a topoisomerase I inhibitor. In preclinical studies, GenSci139 demonstrated broad-spectrum efficacy, surpassing ENHERTU in HER2-low tumor models. It also displayed a favorable pharmacokinetic and a tolerable safety profile. These findings support further clinical evaluation of GenSci139 in urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), gastric cancer (GC), triple-negative breast cancer (TNBC) and other EGFR/HER2-driven malignancies. **Methods:** This first-in-human, open-label study (NCT07230977) comprises a dose escalation phase with backfill (Part 1) and a dose expansion phase (Part 2). Part 1 employs an accelerated titration followed by a “3+3” design to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE). Backfill cohorts will be enrolled at selected dose levels according to predefined criteria. Part 2 will further evaluate preliminary antitumor activities in predefined cohorts. Key eligibility criteria include advanced solid tumors, measurable disease per RECIST1.1, adequate hematologic and organ function, being able to provide tumor tissues. GenSci139 is administered intravenously every 3 weeks until disease progression, unacceptable toxicity, withdrawal of consent, initiation of alternative anticancer therapy, or other discontinuation criteria are met. Primary endpoints in Part 1 include the incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs). After determination of the MTD/RDE, Part 2 will evaluate the preliminary anti-tumor activity of GenSci139, with primary endpoints including objective response rate (ORR), disease control rate (DCR) and Duration of response (DoR). The study initiated in December 2025 and is currently recruiting. Clinical trial information: NCT07230977. Research Sponsor: None.

An open-label phase 1 study of DCC-2812 monotherapy in patients with advanced genitourinary cancers.

Ildefonso I. Rodriguez Rivera, Bicky Thapa, Charles M. Psinos, Julia Jennings, Binfeng Xia, Luis A. Carvajal, Aaron Rudeen, Gada Al-Ani, Matthew L. Sherman, Frederic J. Reu, Andrae Vandross; NEXT Oncology, San Antonio, TX; Dana-Farber Cancer Institute, Boston, MA; Deciphera Pharmaceuticals, LLC, Waltham, MA; NEXT Oncology, Austin, TX

Background: The integrated stress response (ISR) is a major adaptive cellular response pathway that cancer cells depend on to survive in the context of oncogenic pathway activation and high proliferative demand. The ISR is tightly regulated by stress-sensing kinases, including general control nonderepressible 2 (GCN2). Under a controllable level of cellular stress, moderate activation of GCN2 promotes adaptation to nutrient and oxygen deficiency, supporting cancer cell survival. In contrast, excessive GCN2 activation in response to unresolvable stress leads to the induction of pro-apoptotic genes and cancer cell death, making pharmacologic activation of this pathway a promising therapeutic strategy. DCC-2812 is an investigational, potent, and selective activator of GCN2 and the ISR pathway in cancer cells. In preclinical studies, DCC-2812 upregulated the ISR pathway and demonstrated single-agent antitumor activity in a variety of cancer cell lines, including those of renal and urothelial origin. DCC-2812 also inhibited tumor growth in vivo in xenograft models of renal cell carcinoma (RCC) and urothelial cell carcinoma. Here, we describe an ongoing phase 1 study evaluating DCC-2812 as a monotherapy in patients with advanced genitourinary cancers. **Methods:** This is a multicenter, open-label, phase 1 dose-escalation study evaluating the safety and preliminary antitumor activity of DCC-2812 in adult patients (≥ 18 years) with histologically or cytologically confirmed advanced or metastatic RCC, urothelial cancer, or castration-resistant prostate cancer (NCT06966024). Eligible patients must have experienced disease progression on or be intolerant of standard-of-care therapies and must have adequate organ function as well as the ability to take oral medication. Individuals will be excluded if they received any anticancer therapy (other than luteinizing hormone-releasing hormone agonists/antagonists for prostate cancer) or investigational therapy within a specified timeframe prior to the first dose of DCC-2812, have impaired cardiac function, or had major surgery within 28 days of the first dose of DCC-2812. Enrolled patients will receive DCC-2812 orally in 28-day cycles. The primary outcome measures are the number of patients with dose-limiting toxicities during cycle 1, treatment-emergent adverse events (TEAEs) and serious adverse events, and dose modifications due to TEAEs. Secondary outcome measures include radiographic objective response rate and radiographic duration of response per Response Evaluation Criteria in Solid Tumors version 1.1 and Prostate Cancer Working Group 3 criteria, if applicable, as well as pharmacokinetics. The study is currently recruiting patients at multiple sites in the United States. Clinical trial information: NCT06966024. Research Sponsor: Deciphera Pharmaceuticals, LLC, a member of ONO Pharma.

RNDO-564-001: A first-in-human, phase 1/1b study of RNDO-564, a costimulatory bispecific antibody for the treatment of advanced bladder cancer and other Nectin-4-positive solid tumors.

John D. Powderly II, Starlynn Clarke, Udaya Rangaswamy, Katherine E. Harris, Lynnae Jackson, Thomas Manley, Sreenivasa R. Chandana, Drew W. Rasco, William Bennion McKean, Neal D. Shore, Benjamin Garmez; Carolina BioOncology Institute PLLC, Huntersville, NC; Rondo Therapeutics, Hayward, CA; Rondo Therapeutics, Inc., Hayward, CA; START Midwest, Grand Rapids, MI; START San Antonio, San Antonio, TX; Utah Cancer Specialists, START Mountain Region, West Valley City, UT; START Carolinas/Carolina Urologic Research Center, Myrtle Beach, SC; Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN

Background: RNDO-564 is a novel CD28 x Nectin-4 bispecific antibody (bsAb) with high affinity Nectin-4 binding and optimized CD28 costimulatory arms designed to maximize the therapeutic window. RNDO-564-001 (NCT07218003) is an ongoing, open label, multicenter, phase 1/1b dose escalation and dose optimization study of RNDO-564 as monotherapy, and in combination with pembrolizumab (anti-programmed death PD-1 monoclonal antibody), in adults with relapsed/refractory (R/R), locally advanced or metastatic urothelial cancer (la/mUC) and other Nectin-4 positive solid tumors. **Methods:** The objectives of the study are to assess the safety, tolerability, and to determine the recommended phase 2 dose (RP2D) of intravenous RNDO-564 monotherapy given on Days 1, 8, and 15 of a 21-day cycle. Monotherapy dose escalation will include an accelerated titration component using four single participant (pt) cohorts, followed by more gradual dose increments using a Bayesian Optimal Interval (BOIN) with backfill design. Pts with R/R la/mUC, cervical, head and neck, esophageal, gastric, gastroesophageal, non-small cell lung, or triple negative breast cancer, who have exhausted, are ineligible for, or declined available standard treatment options, are eligible for the dose escalation phase of the study. Pts must have an ECOG performance status of 0-1. Pts with prior Nectin-4 directed therapies and Monomethyl Auristatin E (MMAE) exposure and those with ongoing Grade ≤ 2 peripheral neuropathy are eligible. Pts with a history of, or with active, inflammatory skin conditions are ineligible. Enrollment into Cohorts 1 and 2 have been completed without dose limiting toxicity (DLT). Enrollment to cohort 3 opened in January 2026. Safety endpoints include incidence of adverse events per CTCAE v6.0. Secondary endpoints include clinical activity, pharmacokinetics, and incidence of anti-drug antibody development. Retrospective assessment of Nectin-4 expression on tumor tissue by immunohistochemistry (IHC), and measurement of CD28 receptor occupancy, T cell activation, and serum cytokines in peripheral blood will be performed as exploratory endpoints. To determine the optimal RP2D in R/R la/mUC, up to two 20 pt dose optimization cohorts at two different dose levels will be enrolled. Separate dose escalation and optimization stages in combination with pembrolizumab will be conducted to assess safety, clinical activity, and RP2D for further development of combination treatment. Based on emerging clinical data, additional monotherapy and/or combination therapy expansion cohorts may be opened for pts with non-UC Nectin-4 positive solid tumors. **Conclusions:** RNDO-564-001 is an ongoing phase 1/1b study to determine the safety, tolerability, clinical activity, and RP2D of RNDO-564 in R/R la/mUC and other Nectin-4 positive solid tumors. Clinical trial information: NCT#07218003. Research Sponsor: Rondo Therapeutics, Inc.

A phase III randomized trial of pembrolizumab in combination with sacituzumab govitecan vs standard of care in anti-PD-(L)1-resistant advanced urothelial cancer: ECOG-ACRIN EA8231.

Monika Joshi, Se Eun Kim, Petros Grivas, Elizabeth Wulff, Alicia K. Morgans, Kriti Mittal, Joshua Warrick, Melissa A. Reimers, Noah M. Hahn, Naomi Balzer Haas, Lynne I. Wagner, Michael A. Carducci; Penn State Cancer Institute, Hershey, PA; Dana-Farber Cancer Institute-ECOG-ACRIN Biostatistics Center, Boston, MA; Department of Medicine, Division of Hematology/Oncology, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; University of Kansas Medical Center, Kansas City, KS; Dana-Farber Cancer Institute, Boston, MA; UMass Chan Medical School, Worcester, MA; Yale School of Medicine, New Haven, CT; Division of Oncology, Department of Internal Medicine, Washington University in St. Louis, St. Louis, MO; The Johns Hopkins University School of Medicine, Baltimore, MD; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; The University of North Carolina at Chapel Hill, Winston-Salem, NC; Johns Hopkins, Baltimore, MD

Background: Patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) who progress after anti-PD-(L)1 therapy (CPI-R) and enfortumab vedotin (EV) have relatively limited treatment options and poor outcomes. SG, a TROP-2-directed antibody-drug conjugate (ADC), has meaningful efficacy in previously treated la/mUC, while SG plus pembro achieved 41% overall response rate (ORR; 20% complete response rate) in platinum-refractory la/mUC. With rapidly evolving treatment paradigms and earlier use of EV and anti-PD(L)1, the frequency of CPI-R la/mUC is expected to increase; therefore, newer combinations and the role of anti-PD(L)1 re-challenge should be prospectively evaluated in previously treated la/mUC. We hypothesized that SG/pembro combination would improve outcomes over standard chemotherapy (SOC) in pts previously treated with anti-PD(L)1.

Methods: EA8231 is an open-label, multicenter, randomized phase III trial enrolling adults with unresectable la/mUC. Key eligibility criteria: a) ECOG PS 0-2 b) Prior anti-PD(L)1 given in any disease setting but no cancer progression within 12 weeks from starting prior anti-PD(L)1 initiation c) Prior exposure to EV unless contraindicated d) ≥ 1 lines of systemic therapy for la/mUC [FGFR3 altered tumors must have received prior FGFR inhibitor unless contraindicated] e) Bellmunt score 0-2 f) No prior exposure to SG or other TROP-2 directed therapies or drugs containing topo-isomerase I inhibitor. Treatment: Pts are randomized 1:1 to Arm A SOC (platinum-gemcitabine or taxane Q3 week cycle) OR Arm B pembro/SG (Pembro 200mg on day 1 + SG 10mg/kg on days 1, 8 of a 21-day cycle with G-CSF support). Pts are stratified by Bellmunt score (0-1 vs 2), prior lines of therapy (≤ 2 vs > 2), prior exposure to platinum-based chemotherapy (yes vs no prior exposure and platinum-eligible vs no prior exposure and platinum-ineligible), duration of prior anti PD-(L)1 therapy (≤ 6 vs > 6 months). G-CSF primary prophylaxis is strongly recommended, esp. with SG. **Endpoints:** Primary endpoint: overall survival (OS); secondary endpoints: progression-free survival, ORR, clinical benefit rate, duration of response, safety/tolerability, health related QOL (NFBISI-18; FACIT-Fatigue; EQ-5D-5L). Statistical plan: Trial is designed to demonstrate 42.5% improvement in median OS [platinum-ineligible cohort: median OS increase from 9 to 12.8 months; platinum-eligible cohort: median OS increase from 10.3 to 14.7 months]; 80% power with 1-sided 0.025 type I error rate; HR (pembro+SG/SOC) 0.70, N=320. Trial Status: Activation date: 10/23/2025 (1 patient accrued as of Jan 6, 2026; 28 approved sites, additional sites pending). Clinical trial information: NCT06524544. Research Sponsor: National Cancer Institute of the National Institutes of Health under award numbers: U10CA180820, U10CA180794, U10CA180821, UG1CA233180, UG1CA233196, UG1CA233328, UG1CA233339, and UG1CA233373.

TROPION-Urothelial03: A phase 2/3 study of datopotamab deruxtecan (Dato-DXd) + platinum chemotherapy (CT) vs gemcitabine + platinum CT in participants with locally advanced or metastatic urothelial carcinoma (la/mUC) with progression on or after enfortumab vedotin (EV) + pembrolizumab.

Matthew D. Galsky, Alexandra Drakaki, Arnab Basu, Bradley Alexander McGregor, Jens Bedke, Yohann Loriot, Eiji Kikuchi, Jun Guo, Benjamin Garmez, Srikala S. Sridhar, Gunnar Klauss, Daisy Lin, Chelsea Liu, Andrea B. Apolo, Thomas Powles; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; UCLA Health, Los Angeles, CA; Division of Hematology and Oncology, Mayo Clinic Florida, Jacksonville, FL; Dana Farber/Harvard Cancer Center, Boston, MA; Klinikum Stuttgart Katharinen Hospital, Stuttgart, Germany; Gustave Roussy Cancer Institute, Paris, France; St. Marianna University School of Medicine, Kawasaki, Japan; Peking University Cancer Hospital and Research Institute, Beijing, China; Sarah Cannon Research Institute, Nashville, TN; Princess Margaret Cancer Centre, Toronto, ON, Canada; Daiichi Sankyo, Inc., Basking Ridge, NJ; National Cancer Institute, National Institutes of Health, Bethesda, MD; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom

Background: Although first-line (1L) EV + pembrolizumab has improved outcomes for patients with la/mUC, most experience disease progression, highlighting an unmet need for novel therapies. TROP2 is a glycoprotein highly expressed in several epithelial tumors, including UC. Dato-DXd is a TROP2-directed antibody–drug conjugate comprising an anti-TROP2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload (DXd), designed to induce selective tumor-cell death and reduce systemic exposure to the payload. Dato-DXd has demonstrated durable efficacy and a manageable safety profile in patients with la/mUC both as monotherapy (TROPION-PanTumor01 [NCT03401385]) and in combination with immunotherapy (TROPION-PanTumor03 [NCT05489211]). We describe a Phase 2/3 trial comparing the efficacy and safety of Dato-DXd + platinum CT (carboplatin or cisplatin) vs gemcitabine + platinum CT in participants with la/mUC with disease progression on or after EV + pembrolizumab. **Methods:** TROPION-Urothelial03 (NCT07129993) is a global, multicenter, randomized, open-label, Phase 2/3 trial. In Part A (Phase 2), ~60 participants will be randomized 1:1 to receive Dato-DXd 4 or 6 mg/kg + platinum CT. In Part B (Phase 3), ~570 participants will be randomized 1:1 to receive Dato-DXd at the recommended Phase 3 dose (determined using Part A data) + platinum CT vs gemcitabine + platinum CT. Randomization in Part A is stratified by assignment of platinum CT (carboplatin vs cisplatin), and in Part B, by assignment of platinum CT, presence vs absence of liver metastasis at screening, and time to progression on 1L EV + pembrolizumab (<6 vs ≥6 months). Study treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or other reasons per protocol. Radiographic tumor assessments occur every 6 weeks for 54 weeks, then every 12 weeks. The primary endpoint of Part A is objective response rate (ORR) by investigator per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1). The dual primary endpoints of Part B are progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1 and overall survival (OS). Secondary endpoints include duration of response by investigator per RECIST 1.1 (Part A), and PFS by investigator per RECIST 1.1 and ORR by BICR and investigator per RECIST 1.1 (Part B). In Part A, ORR will be summarized with 2-sided 95% exact confidence intervals using the Clopper–Pearson method by trial group. In Part B, PFS and OS will be compared between trial groups using a log-rank test stratified by randomization stratification factors, with hazard ratios from the stratified Cox regression model. Clinical trial information: NCT07129993. Research Sponsor: Daiichi Sankyo, Inc.

Advancing treatment of low-grade upper tract urothelial carcinoma (LG UTUC) with padeliporfin vascular-targeted photodynamic therapy (VTP): The ENLIGHTED phase 3 trial.

Vitaly Margulis, Ronald Kaufman Jr., Jay D. Raman, Hooman Djaladat, Ahmad Shabsigh, Asaf Shvero, Sarah P. Psutka, Gautier Marcq, Neal D. Shore, Edward M. Uchio, Steffen Rausch, Marcos Aller, Robert Grubb, Kenneth Ogan, Nirmish Singla, Petro Savchenko, Ladislav Pecan, Genia Alpert, Avigdor Joshua Scherz, Jonathan Coleman; Department of Urology, UT Southwestern Medical Center, Dallas, TX; Albany Medical College, Albany, NY; Milton S. Hershey Medical Center, Hershey, PA; Department of Urology, USC/Norris Comprehensive Cancer Center, Laton, CA; Ohio State University Comprehensive Cancer Center, Columbus, OH; "Chaim Sheba" Medical Center, Ramat Gan, Israel; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; Lille University Hospital, Lille, France; Carolina Urologic Research Center, Myrtle Beach, SC; University of California, Irvine, Irvine, CA; Eberhard Karls University Tübingen, Tübingen, Germany; Hospital Universitario de A Coruna, Coruna, Spain; Medical University of South Carolina, Charleston, SC; Emory University School of Medicine Winship Cancer Institute, Atlanta, GA; Johns Hopkins Brady Urological Institute, Baltimore, MD; Steba France SAS, Versailles, France; Steba/ImPact Biotech Ltd, Ness Ziona, Israel; Weizmann Institute of Science, Rehovot, Israel; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Padeliporfin VTP is a drug-led combination therapy consisting of IV Padeliporfin activated by a low-power near-infrared (753 nm) laser-fiber system. A non-contact cylindrical fiber positioned near the tumor provides circumferential illumination, inducing vascular occlusion and coagulative tumor necrosis while preserving tissue structure. Safety and efficacy were shown in a Phase 1 UTUC study (NCT03617003). We report emerging efficacy, durability, and safety from the ENLIGHTED Phase 3 trial in LG UTUC (NCT04620239). **Methods:** ENLIGHTED is an open-label Phase 3 study conducted in the US, EU, and Israel, evaluating the efficacy, durability, and safety of padeliporfin VTP in LG UTUC. Eligible patients (pts) may have new or recurrent disease, be treatment-naïve or previously treated, and have up to two biopsy-confirmed LG lesions (5–15 mm kidney or 5–20 mm ureter) without high-grade cells on instrumented cytology. VTP is performed via retrograde upper tract endoscopy under anesthesia and low-light conditions. Padeliporfin is administered IV, and an optical fiber with a 20–40 mm diffuser is positioned near the tumor through the scope, followed by 10 minutes of laser illumination. Treatment consists of an Induction Treatment Phase (ITP) of 1–3 VTP sessions at 4-week intervals until complete response (CR) or treatment failure at Primary Response Evaluation (PRE). Pts achieving CR enter a 12-month Maintenance Treatment Phase (MTP) with quarterly endoscopic surveillance and retreatment for treatable recurrences, followed by long-term follow-up up to 48 months. The primary endpoint is CR at PRE (28 ± 3 days post last ITP treatment), defined by absence of visible tumor on endoscopy and negative instrumented cytology. A total of 100 pts are to be enrolled. As of January 19, 2026, 78 pts were enrolled and 63 completed ITP. Response rates were: CR 73.0%, PR 17.7%, DR 3.2%, PD 4.8%, and stable disease 1.6%. Among pts with CR at PRE, 39.5% had completed MTP by data cutoff, with 88.2% maintaining CR in the treated area (TA) for ≥12 mos. Median Duration of Response in the TA was not reached and is ≥23.9 mos. Most pts remains in MTP or follow-up. The most common treatment-emergent adverse events were hematuria (10.6%), flank pain (8.6%), nausea (5.5%), procedural pain (4.5%), abdominal pain (4.1%), dysuria (4.1%), vomiting (3.4%), and fatigue (3.1%), all Grade 1–2 with a median duration of 5 days. 23 serious adverse events (7.7%) were reported, mostly unrelated to treatment. One Grade 3 SAE (renal colic related to VTP) resolved within 2 days. Padeliporfin VTP demonstrates favorable preliminary efficacy, durable responses, and a safety profile consistent with prior experience. Enrollment is ongoing, and final outcomes are anticipated to support regulatory approval of an organ-preserving therapy for LG UTUC. Clinical trial information: NCT04620239. Research Sponsor: Steba/Impact biotech.

Selective bladder-sparing trial with sasanlimab as maintenance treatment based on clinical response to neoadjuvant treatment in molecularly categorized muscle invasive bladder cancer patients: SASAN-SPARING trial.

Elena Sevillano, Tatiana P. Grazioso, Alfonso Gomez De Liaño Lista, Pablo Gajate, Nuria Lainez, Miguel A. Climent Duran, Julia Martinez Perez, Jesus Garcia-Donas, Juan Francisco Rodriguez-Moreno, Arantzazu Barquin, Xavier Garcia del Muro, Javier Puente, Oscar Reig Torras, Diego Losada, Guillermo de Velasco; HM Sanchinarro Centro Integral Oncologico Clara Campal (CIOCC), Madrid, Spain; Medical Oncology, Laboratorio de Innovación en Oncología, Unidad de Tumores Ginecológicos, Genitourinarios y de Piel, HM CIOCC Madrid (Centro Integral Oncológico Clara Campal), Instituto de Investigación Sanitaria HM Hospitales, Madrid, Spain; Medical Oncology Department - Complejo Hospitalario Universitario Insular-Materno Infantil, Universidad de Las Palmas de Gran Canaria, Las Palmas De Gran Canaria, Spain; Medical Oncology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; Medical Oncology, Hospital Universitario de Navarra, Pamplona, Spain; Fundación Instituto Valenciano de Oncología, Valencia, Spain; Department of Medical Oncology, Hospital Universitario Virgen del Rocío, Seville, Spain; Hospital Universitario HM Sanchinarro – CIOCC, Madrid, Spain; Medical Oncology Department, Institut Català d'Oncologia IDIBELL Research Institute, University of Barcelona, Barcelona, Spain; Hospital Clínico San Carlos, Madrid, 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; University Hospital 12 de Octubre, Madrid, Spain

Background: Muscle-invasive bladder cancer (MIBC) is an aggressive disease with a high risk of progression, for which radical cystectomy (RC) remains the standard of care. Adaptive bladder-sparing strategies based on post-neoadjuvant clinical restaging are increasingly explored to maintain oncologic control while preserving quality of life. SASAN-SPARING evaluates sasanlimab, a PD-1 inhibitor, as maintenance therapy in patients achieving a clinical response after neoadjuvant cisplatin-based chemotherapy. **Methods:** SASAN-SPARING (HM-8788561; NCT06623162) is an ongoing, single-arm, multicenter, phase II trial enrolling patients aged ≥ 18 years with treatment-naïve, localized MIBC (pT2–T4a, No, Mo) eligible for neoadjuvant chemotherapy. All patients receive four cycles of cisplatin (70 mg/m² on day 1) plus gemcitabine (1000 mg/m² on days 1 and 8) every 3 weeks, followed by comprehensive clinical restaging. Patients achieving a clinical response (cT0/Ta/T1/Tis, negative cytology, and negative imaging) are eligible for bladder preservation with sasanlimab 300 mg administered subcutaneously every 4 weeks for up to 12 cycles. Non-responders ($\geq$ cT2) undergo RC. During maintenance, restaging is performed every 12 weeks, and RC may be considered upon loss of response or disease progression. The primary endpoint is bladder-intact overall survival at 12 months after the first dose of sasanlimab. Secondary endpoints include disease-free survival, metastasis-free survival, overall survival, safety, and health-related quality of life. The study incorporates an ambitious biomarker analysis, including whole-genome sequencing of tumour tissue and plasma, the use of ctDNA in plasma and urine for tumour assessment and molecular dynamics, and the study of the gut microbiome in stool. Biomarker-correlative studies will provide a valuable tool for personalized treatments and inform treatment decisions in adaptive strategies such as SASAN-SPARING. The Expected sample size is 70 patients, assuming a 12-month biOS of 81% (H0) and an increase with sasanlimab up to 93% (H1) (one-arm survival test; $\alpha=0.05$ $\beta=0.8$). Recruitment began in December 2024. As of January 2026, 62 patients have been enrolled across 10 centers, and 21 started sasanlimab maintenance therapy. Enrollment is ongoing. SASAN-SPARING explores an adaptive, biomarker-integrated bladder-sparing strategy which aims to generate prospective evidence to support organ-preservation strategies in MIBC. Clinical trial information: NCT06623162. Research Sponsor: None.