431 **General Session**

Positive efficacy and safety phase 3 results in both CIS and papillary cohorts BCG-unresponsive nonmuscle invasive bladder cancer (NMIBC) after IL-15RαFc superagonist N-803 (Anktiva) and BCG infusion.

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Background: N-803, a high affinity IL-15 immunostimulatory fusion protein promotes proliferation and activation of natural killer (NK) cells and CD8+ T cells, but not T reg cells. Phase 1b trial demonstrated that intravesical N-803 with BCG induced complete response in all BCG-Naïve NMIBC patients, without recurrences for 24 months. An open-label, multicenter Phase 3 study (QUILT 3.032) of intravesical BCG plus N-803 in patients with BCG-unresponsive high-grade NMIBC (NCT03022825) with CIS and Papillary disease is reported. At ASCO GU 2021 we reported on CIS Cohort A and report here the full enrollment of CIS (n = 81), interim analysis of Papillary Cohort B (n = 73) and the combined efficacy and safety results in BCG unresponsive NMIBC (n = 154). **Methods:** All treated patients received intravesical N-803 plus BCG. The primary endpoints for papillary and CIS are disease free rate at 12 months and complete response respectively. Secondary endpoints are duration of response and cystectomy free rate. **Results:** Cohort A (CIS) Efficacy**:** Fully enrolled n = 81 with a 20.9 month median follow-up. CR rate 72% (95% CI: 60.5%, 81.1%) with median duration for 3-month responders of 24.1 months and a 60% probability of maintaining this CR for ≥ 18-months (95% CI: 43.1%, 73.5%). 12-month cystectomy free rate is 89% (95% CI: 80.1%, 94.6%), with a 100% cancer specific survival at 24-months. Cohort B (Papillary) Efficacy**:** To date, 73 patients have enrolled with a median follow-up of 17.3 months. The primary endpoint was met with a disease free rate at 12-months is 57% (95% CI: 43.7%, 68.5%) and at 18-months 53% (95% CI: 38.8%, 64.8%). 12-month cystectomy free rate is 95% (95% CI: 84.7%, 98.3%), with a 98% cancer specific survival at 24-months. Combined Efficacy: In the combined group (n = 154) of BCG unresponsive NMIBC, with a 19.3 months median follow-up, the 12 month cystectomy free rate was 92% (95% CI: 85.5%, 95.3%) and the 24 month OS is 94% (95% CI: 86.9%, 97.1%) with 99.5% cancer specific overall survival. Combined Safety: There were 0% treatment related SAE's and 0% immune related SAE's, with 4/ 154 (3%) ≥ TR Grade 3 AEs. 0% treatment related deaths have occurred as of Sept 2021 analysis date. **Conclusions:** N-803 and BCG was safe and well tolerated with zero percent treatment related or immune related SAEs. The primary end points of both CIS and Papillary disease were met with CR rate of 72% and 12 month Disease free rate of 57% respectively. Durable responses were noted in both cohorts and the therapy resulted in significant avoidance of cystectomy with a cystectomy free rate of 92% and a 24 month cancer specific survival of 99.5% Given the observed strong efficacy and favorable AE profile and mode of administration, N-803 represents a significant advance in the treatment option compared to existing therapies for BCG unresponsive CIS and Papillary NMIBC. Clinical trial information: NCT03022825. Research Sponsor: ImmunityBio.

First-line pembrolizumab (pembro) with or without lenvatinib (lenva) in patients with advanced urothelial carcinoma (LEAP-011): A phase 3, randomized, double-blind study.

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Background: Pembro monotherapy is a standard of care for advanced urothelial carcinoma (UC) and showed antitumor activity and acceptable safety when combined with lenva in the phase 1b/2 KEYNOTE-146 study. We present results of LEAP-011 (NCT03898180), a randomized, double-blind, multicenter, global, phase 3 study of first-line pembro + lenva vs pembro + placebo in pts with locally advanced or metastatic UC who are cisplatin-ineligible with PD-L1–positive tumors or are ineligible to receive platinum-based chemotherapy. **Methods:** Adults with histologically confirmed, locally advanced/unresectable or metastatic UC who were cisplatin-ineligible with tumors expressing PD-L1 (combined positive score ≥10) or were ineligible to receive platinum-based chemotherapy regardless of PD-L1 status were randomly assigned 1:1 to receive pembro 200 mg IV Q3W for up to 35 cycles (~2 y) + either lenva 20 mg orally once daily or placebo. Primary end points were PFS per RECIST v1.1 and OS. The key secondary end point was ORR per RECIST v1.1. An independent data monitoring committee (DMC) regularly reviewed safety data every 3 months; for the 6th review, a nonbinding futility analysis to evaluate ORR (−1%) and PFS (HR ≥1.1) was performed. There was no futility bound for OS. **Results:** Of 441 randomly assigned pts, 218 were assigned to receive pembro + lenva (median age, 74 y [range, 43-93]; ECOG PS 2, 83.5%) and 223 (median age, 73 y [range, 47-92]; ECOG PS 2, 83.0%) were assigned to receive pembro + placebo. Median duration of treatment was 3.8 mo (range, 0.0-20.7) for pembro + lenva and 3.4 mo (range, 0.0-22.0) for pembro + placebo. Median PFS was 4.2 mo (95% CI, 3.8-5.9) in the pembro + lenva group and 4.0 mo (95% CI, 2.7-5.4) in the pembro + placebo group (HR, 0.91 [95% CI, 0.71-1.16]). Median OS was 11.2 mo (95% CI, 7.4-14.9) with pembro + lenva vs 13.8 mo (95% CI, 9.8-18.8) with pembro + placebo (HR, 1.25 [95% CI, 0.94-1.67]; 6-mo OS rate, 63.6% vs 70.7%). ORR was 31.2% with pembro + lenva vs 26.5% with pembro + placebo. In 436 treated pts, treatment-related AEs (TRAEs) occurred in 186 of 214 pts (86.9%) in the pembro + lenva group and in 149 of 222 pts (67.1%) in the pembro + placebo group. Grade 3-5 TRAEs occurred in 107 pts (50.0%) in the pembro + lenva group and in 62 pts (27.9%) in the pembro + placebo group. Death from a TRAE occurred in 6 pts (2.8%) in the pembro + lenva group and in 1 pt (0.5%) in the pembro + placebo group. **Conclusions:** The safety profile of pembro + lenva was consistent with that of previous studies; no new safety signals were observed. The benefit/risk ratio for pembro + lenva was not considered positive vs pembro + placebo in platinum-ineligible pts with advanced UC. Antitumor activity of pembro + placebo was similar to what has been reported in previous studies, and pembro monotherapy remains standard of care as first-line therapy in platinum-ineligible pts with advanced UC. Clinical trial information: NCT03898180. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Eisai Inc., Woodcliff Lake, NJ, USA.

433 **General Session**

Multi-institutional matched comparison of radical cystectomy to trimodality therapy for muscle-invasive bladder cancer.

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Background: Prior randomized controlled trials (RCT) comparing bladder preservation to radical cystectomy (RC) for muscle invasive bladder cancer (MIBC) closed early due to lack of accrual. Given that no future RCTs are foreseen, and in the absence of level 1 data, we aimed to provide the best evidence possible on outcomes of matched cohorts comparing trimodality therapy (TMT, maximal transurethral resection of bladder tumor followed by concurrent chemoradiation) to RC in order to guide management. **Methods:** This retrospective analysis included 703 patients with MIBC clinical stage T2-T3/4aN0M0 MIBC urothelial carcinoma of the bladder, 421 RC and 282 TMT who would have been eligible for both TMT or RC, treated at the Massachusetts General Hospital, Boston; Princess Margaret Cancer Centre, Toronto; and University of Southern California, Los Angeles between 2005-2017. To compare homogeneous cohorts, all patients included in this analysis had solitary tumors $<$ 7 cm, no or unilateral hydronephrosis, and no multifocal carcinoma in situ. Treatment propensity scores were estimated using logistic regression, and patients were matched 3:1 with replacement. Covariates included age, sex, clinical T stage, hydronephrosis, (neo)adjuvant chemotherapy, body mass index, smoking history, and ECOG status. Overall survival (OS) was estimated with adjusted Cox models; cancer-specific survival (CSS), distant failure-free survival, pelvic nodal failure-free survival and metastasis-free survival (combined distant and pelvic nodal failure) were estimated with adjusted competing risk models. Our primary endpoint of interest was metastasis-free survival. The analysis was performed as intent-to-treat. **Results:** The 3:1 matched cohort comprised of 1,116 patients (834 RC vs 282 TMT). After matching, age (71.3 vs 71.6), cT2 clinical stage (88 vs 90%), presence of hydronephrosis (12 vs 10%), and use of (neo)adjuvant chemotherapy (60 vs 65%) were similar between RC and TMT cohorts. Salvage cystectomy was performed in 38 patients (13%) treated by TMT. At 5 years, metastasis-free (73 vs 78%, p = 0.07), distant failure-free (78 vs 82%, p = 0.14), and pelvic nodal failure-free (96 vs 94%, p = 0.33) survival were not statistically different between RC and TMT, whereas CSS and OS favored TMT (78 vs 85%, p = 0.02; 70 vs 78%, p $<$ 0.001). Outcomes for RC and TMT were not different among centers. Final pT stage in the RC patients was: pT0 14%, pT1 7%, pT2 29%, pT3/4 42% and N+ 24%. Peri RC mortality was 2.1% and median number of nodes removed was 40. NMIBC recurrence occurred in 57/278 (20.5%) TMT patients. **Conclusions:** This large multi-institutional contemporary study provides the best evidence to date, in the absence of randomized trials, supporting TMT for select patients with MIBC. Oncologic outcomes seem to be equivalent between TMT and RC, affirming the position that TMT should be offered as an effective alternative. Research Sponsor: None.

TROPHY-U-01 Cohort 3: Sacituzumab govitecan (SG) in combination with pembrolizumab (Pembro) in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PLT)-based regimens.

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Background: Checkpoint inhibitors (CPIs) are standard therapy for pts with mUC after PLT-based regimens, with limited long-term disease control. SG is an antibody-drug conjugate composed of an anti-trophoblast cell-surface antigen 2 (Trop-2) antibody coupled to SN-38 (a topoisomerase-I inhibitor) via a proprietary hydrolyzable linker. In the TROPHY-U-01 registrational phase 2 trial, SG monotherapy demonstrated significant activity and manageable safety in pts with mUC who progressed after prior PLT-based chemotherapy and CPI, with 27% objective response rate (ORR) and median overall survival of 11 months (Tagawa, et al. *J Clin Oncol.* 2021). Here, we present interim efficacy and safety results of combining SG with Pembro as 2nd-line therapy in CPI-naive pts with mUC who progressed after PLT-based chemotherapy (cohort 3). **Methods:** TROPHY-U-01 is a multicohort, open-label, global phase 2 trial. Eligible pts had measurable disease, Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, and creatinine clearance ≥30 mL/min. The recommended phase 2 dose (RP2D) was determined during a 10-pt safety lead-in, and additional pts were enrolled at the RP2D in a Simon 2-stage design. Primary endpoint: ORR by blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Key secondary endpoints: investigator-assessed ORR, clinical benefit rate [CBR; complete response (CR) + partial response (PR) + stable disease], progression-free survival (PFS), and safety. **Results:** At the time of data cutoff, 41 pts received at least a dose of SG at the RP2D (10 mg/kg). Of these 41 pts, median (range) age was 67y (46–86), 83% men, 61% ECOG PS 1, 76% had ≥1 Bellmunt risk factor, and median (range) number of prior anticancer regimens was 1 (1–3). At a median follow-up of 5.8 mo, the investigator-assessed ORR was 34% (95% CI, 20.1–50.6; 1 CR; 13 PR); CBR was 44% (95% CI, 28.5–60.3); 6-mo PFS rate was 47%. Median time to response was 2.0 mo (95% CI, 1.3–2.8). Most common treatment-emergent adverse events (TEAEs) were diarrhea (76%), nausea (59%), anemia (56%), neutropenia (44%), and asthenia (41%). Treatment-related grade ≥3 AEs occurred in 59% of pts. Key grade ≥3 TEAEs of any cause included diarrhea (24%), anemia (20%), febrile neutropenia (10%), fatigue (7%), and asthenia (5%). Two pts discontinued treatment due to treatment-related AEs. No treatment-related death occurred. **Conclusions:** SG in combination with Pembro demonstrated encouraging ORR and CBR, with an overall manageable safety profile with no new safety signal in CPI-naive pts who progressed after prior PLT-based chemotherapy. The data support further evaluation of SG plus CPI in mUC. Limitations: small sample size, short follow-up, and lack of randomization. Biomarker evaluation is ongoing. Clinical trial information: NCT03547973. Research Sponsor: Gilead Sciences, Inc.

435 **Oral Abstract Session**

Study EV-103 Cohort H: Antitumor activity of neoadjuvant treatment with enfortumab vedotin monotherapy in patients (pts) with muscle invasive bladder cancer (MIBC) who are cisplatin-ineligible.

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Background: Up to 25% of all pts diagnosed with urothelial cancer present with muscle-invasive disease for whom the risk of progression or metastasis is substantial. Neoadjuvant chemotherapy prior to radical cystectomy and pelvic lymph node dissection (RC+PLND) has been shown to prolong overall survival for patients who are cisplatin (cis) eligible. The standard of care for cis-ineligible pts undergoing surgery does not include neoadjuvant therapy. Therefore, safe, and effective neoadjuvant therapies are an unmet need for cis-ineligible pts with MIBC. Enfortumab vedotin (EV) is an antibody-drug conjugate directed to Nectin-4, which is highly expressed in urothelial cancer, and has been shown to benefit locally advanced or metastatic urothelial cancer pts in Phase II and III trials, including cis-ineligible pts. **Methods:** Cohort H of the EV-103 phase 1b/2 trial (NCT03288545) enrolled pts with cis-ineligible cT2-T4aN0M0 MIBC who were eligible for RC+PLND and had an ECOG of 0-2. Pts received 3 cycles of neoadjuvant EV (1.25 mg/kg) on Days 1 and 8 of every 3-week cycle prior to RC+PLND. The primary endpoint of the study was pathological complete response rate (pCRR; ypT0N0) by central review. Key secondary endpoints included pathological downstaging (pDS) rate (yp T0,Tis,Ta,T1,N0) and safety. Results from a preliminary analysis are presented. Results: 22 pts were treated. Pts had cT2 (68.2%), cT3 (27.3%), and cT4 (4.5%) tumors. 68.2% pts had predominant urothelial cancer; 31.8% had a mixed histology. 19 pts completed all 3 cycles of EV. 21 underwent RC+PLND, and 1 had a partial cystectomy. 36.4% pts had a pCR. pDS was seen in 50.0% pts, with 1 case pending central pathology review. The most common EV treatment-related adverse events (TRAEs) were fatigue (45.5%), alopecia (36.4%), and dysgeusia (36.4%). 18.2% pts had Grade $\geq$3 EV TRAEs. No surgeries were delayed due to EV administration. 3 pts had Grade 5 AEs while on study that were unrelated to EV; in 2 pts these AEs occurred $>$ 30 days after RC+PLND. Conclusions: Observed pCRR after neoadjuvant EV showed promising activity in cis-ineligible pts with MIBC who have a high unmet need. Adverse events were consistent with the known safety profile of EV. This first disclosure of data supports the ongoing Phase II and III programs evaluating EV in MIBC. Clinical trial information: NCT03288545. Research Sponsor: Astellas and Seagen Inc.

A randomized, double blind, biomarker selected, phase II clinical trial of maintenance PARP inhibition following chemotherapy for metastatic urothelial carcinoma (mUC): Final analysis of the ATLANTIS rucaparib arm.

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Background: A subset of mUC exhibits a DNA repair deficiency (DRD) phenotype predicting benefit from platinum based chemotherapy (PBC). We hypothesised that switch maintenance therapy with the PARP inhibitor rucaparib, in patients who have derived clinical benefit from PBC, would improve outcomes for patients with mUC harbouring a DRD biomarker. **Methods:** ATLANTIS is an adaptive, multicomparison, phase II trial platform. It tests multiple biomarker selected maintenance therapies for mUC after 4 to 8 PBC cycles without disease progression. Biomarker allocation to the rucaparib comparison was based on ≥10% genomic loss of heterozygosity (%LOH) and/or somatic alteration in defined DRD associated genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*) and/or germline *BRCA1* or *BRCA2* alteration. Biomarker positive patients were randomised (1:1) to maintenance rucaparib 600 mg BID PO, or matched placebo, within 10 weeks of completing PBC, until disease progression. The primary endpoint was progression free survival (PFS). Statistical analysis (data cut 17/Nov/2021) was pre-planned to target a hazard ratio of 0.5. We selected a 20% 1-sided alpha for this signal seeking phase II trial with 85.4% power (requiring 30 PFS events in 40 patients). PFS (RECIST 1.1) was compared between trial arms, by intention to treat, within a Cox model incorporating baseline minimisation factors. Adverse events (AE) were assessed by CTCAE v4.03. **Results:** 74 of 279 (26.5%) screened patients were biomarker positive. 40 were randomised within the rucaparib comparison (Dec 2017-Dec 2020). Biomarker positive status was by high %LOH in 22 (55%), DRD gene alteration in 11 (27.5%) and both in 7 (17.5%). Patient characteristics (median age 70.5; 82.5% male; 87.5% bladder primary; 52.5% ECOG PS 0; 62.5% prior cisplatin; 45% visceral metastases) were balanced by treatment arm. 12 (60%) and 20 (100%) PFS events have occurred in the rucaparib and placebo arms respectively (median duration follow up 94.6 weeks in those still alive). Median PFS was 35.3 weeks (80% confidence interval (CI) 11.7-35.6) with rucaparib and 15.1 weeks (80% CI 11.9-22.6) with placebo (hazard ratio 0.53, 80% CI 0.30-0.92, 1 sided p = 0.07). In the safety population (n = 39) treatment related adverse events were mostly low grade. Rucaparib was tolerable with a median duration of 10 rucaparib or 6 placebo cycles on treatment. The most frequent treatment related AEs (all grades) of fatigue (63.2% vs 30.0%, p = 0.03), nausea (36.9% vs 5.0%, p = 0.03) and rash (21.1% vs 0%, p = 0.04) were more common with rucaparib respectively. **Conclusions:** Maintenance rucaparib, following PBC, extended PFS in DRD biomarker selected patients with mUC and is tolerable. Further investigation of PARP inhibition for mUC is warranted. Clinical trial information: 25859465. Research Sponsor: Cancer Research UK, Pharmaceutical/Biotech Company.

BAYOU: A phase II, randomized, multicenter, double-blind, study of durvalumab (D) in combination with olaparib (O) for the first-line treatment of platinum-ineligible patients with unresectable, stage IV urothelial carcinoma (UC).

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Background: The prognosis for patients (pts) with advanced UC remains poor, particularly for those unable to tolerate platinum-based chemotherapy. Defects in DNA damage repair (e.g., mutations in homologous recombination repair [HRR] genes) are common in UC and render tumor cells sensitive to poly(ADP-ribose) polymerase (PARP) inhibition. HRR gene mutations (HRRm) and PARP inhibition may enhance the antitumor response of immune checkpoint inhibitors. We conducted a randomized phase II study to evaluate D (anti–PD-L1) in combination with O (a PARP inhibitor) or placebo (P) as a first-line treatment for platinum-ineligible pts with unresectable, stage IV UC (BAYOU; NCT03459846). **Methods:** Eligible pts were an age of ^{3}18 years with an ECOG performance status (PS) of 0, 1, or 2, histologically or cytologically confirmed transitional cell carcinoma, and who had not received prior systemic therapy for unresectable, stage IV disease. Pts were randomized 1:1 to receive D (1500 mg IV q4w) plus O (orally at 300 mg BID) vs D (1500 mg IV q4w) plus O-matching placebo (P). Pts were stratified according to centrally-determined HRR status (mutant vs wild-type) and Bajorin risk index (a composite of visceral metastases and ECOG PS [0, 1 vs 2]). The primary endpoint was progression-free survival (PFS) by RECIST v1.1 (investigator assessed) in the intention-to-treat (ITT) population. Secondary endpoints included overall survival (OS) in the ITT population and PFS in the subset of pts with HRRm. The data cutoff occurred on October 15, 2020. **Results:** A total of 154 pts were randomized to receive D+O (n = 78) or D+P (n = 76). Among all randomized pts at baseline, 17%, 42%, and 40% had an ECOG PS of 0, 1, or 2, respectively, and 20% had an HRRm. Median PFS was not significantly different between D+O and D+P in the ITT population (Table). In the subset of pts with HRRm, median PFS was 5.6 months in the D+O group and 1.8 months in the D+P group (Table). In the ITT population, median OS (95% CI) was 10.2 months (7.0–13.9) in the D+O group and 10.7 months (7.2–17.3) in the D+P group (HR 1.07, 95% CI 0.72–1.61). Among all treated pts, grade 3 or 4 treatment-related adverse events occurred in 18% and 9% in the D+O and D+P groups, respectively, with one death due to anemia in the D+P group. **Conclusions:** The BAYOU study did not meet its primary endpoint. However, the results of pre-planned secondary analyses suggest a potential role for PARP inhibition in UC pts harboring HRRm. No new safety signals were observed. Clinical trial information: NCT03459846. Research Sponsor: AstraZeneca.

Primary and secondary PFS analyses.

	D+O		D+PBO
ITT population	n = 78		n = 76
Median PFS, mo (95% CI)	4.2 (3.6–5.6)		3.5 (1.9–5.1)
HR (95% CI)		0.94 (0.64–1.39)	
Log-rank p-value		0.789	
HRRm subset*	n = 17		n = 14
Median PFS, mo (95% CI)	5.6 (1.9–8.1)		1.8 (1.7–2.2)
HR (95% CI)		0.18 (0.06–0.47)	
Log-rank p-value		< 0.001	

*Secondary analysis.

Primary analysis from DS8201-A-U105: A phase 1b, two-part, open-label study of trastuzumab deruxtecan (T-DXd) with nivolumab (nivo) in patients (pts) with HER2-expressing urothelial carcinoma (UC).

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Background: HER2 overexpression has been found in invasive UC, suggesting a role for HER2 in disease progression and prognosis (Kruger *Int J Oncol* 2002). T-DXd is an antibody-drug conjugate comprising an anti-HER2 antibody, a cleavable linker, and a topoisomerase I inhibitor payload. Preclinical models showed that T-DXd combined with an anti-PD-1 antibody had greater efficacy versus either agent alone (Iwata *Mol Cancer Ther* 2018). We conducted a phase 1b, 2-part, open-label, multicenter study of T-DXd in combination with nivo in pts with HER2-expressing advanced/metastatic UC (NCT03523572). **Methods:** Pts aged ≥18 y had pathologically documented advanced/metastatic UC with centrally confirmed HER2 expression by immunohistochemistry (IHC) 2+/3+ (cohort 3; high expression) or IHC 1+ (cohort 4; low expression) who received prior platinum-based therapy with documented progression. Pts received T-DXd at 5.4 mg/kg and nivo 360 mg IV every 3 weeks (recommended dose for expansion). The primary endpoint was confirmed objective response rate (ORR) assessed by independent central review (ICR) per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary endpoints (assessed by ICR) included duration of response (DOR), progression-free survival (PFS), time to response (TTR), and overall survival (OS), and safety. **Results:** At the primary analysis data cutoff (July 22, 2021), 34 pts (cohort 3, n = 30; cohort 4, n = 4) received T-DXd and nivo. Median age was 70.9 y (range, 41.4-80.5), 88.2% were male, 61.8% received ≥1 prior regimens for locally advanced/metastatic disease, and 26.5% had a history of liver metastases. Median treatment duration (all pts) was 3.2 mo (range, 1-21) for T-DXd and 4.1 mo (range, 1-20) for nivo. In cohort 3, ORR by ICR was 36.7% (95% CI, 19.9-56.1; complete response, 13.3%; partial response, 23.3%), median DOR was 13.1 mo (95% CI, 4.1- NE), median PFS was 6.9 mo (95% CI, 2.7-14.4), median TTR was 1.9 mo (range 1.2-6.9), and median OS was 11.0 mo (95% CI, 7.2-NE). Grade (G) ≥3 treatment-emergent adverse events (TEAEs) occurred in 73.5% of all pts (44.1% related to T-DXd; 26.5% related to nivo). TEAEs leading to drug discontinuation occurred in 32.4% of all pts (17.6% related to T-DXd; 23.5% related to nivo). The most common any-grade TEAEs were nausea (73.5%), fatigue (52.9%), and vomiting (44.1%). Adjudicated drug-related interstitial lung disease (ILD)/pneumonitis occurred in 23.5% of all pts (2 G1; 4 G2; 1 G3; 1 G5). **Conclusions:** T-DXd combined with nivo showed antitumor activity in pts with high-expressing HER2 UC. The safety profile was consistent with prior studies for T-DXd in other indications and nivo monotherapy in UC pts. Adjudicated ILD/pneumonitis was within the range observed in other T-DXd monotherapy studies. Ongoing clinical trials are further exploring T-DXd in this population. Clinical trial information: NCT03523572. Research Sponsor: Daiichi Sankyo, Pharmaceutical/Biotech Company.

First line avelumab in PD-L1+ve metastatic or locally advanced urothelial cancer (aUC) patients unfit for cisplatin (cis): The ARIES trial.

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Background: Avelumab (ave) was approved as maintenance therapy after platinum-based first line (1L) therapy for patients (pts) with aUC based on ph. 3 Javelin Bladder 100 study (NCT02603432), showing significant overall survival (OS) improvement. Here we tested the activity of ave as 1L of therapy in cis-unfit pts with aUC and PD-L1+ve expression. **Methods:** ARIES is a single-arm, multi-site, open-label phase II trial. Enrolled pts had aUC, were cis-unfit (at least one of: ECOG-PS = 2, CrCl $<$ 60 mL/min, grade $\geq$2 peripheral neuropathy/hearing loss, progression within 6-mos before the end of neo/adj chemo), had not previously received chemo for aUC and PD-L1$\geq$5% (SP263) centrally assessed. Pts received ave 10 mg/Kg IV Q2W until progression, unacceptable toxicity and withdrawal, whichever occurred first. The primary endpoint was the 1-year OS. Key secondary endpoints were median-OS, -PFS, ORR and safety. **Results:** A total of 198 eligible cis-unfit pts have been tested for PD-L1 and 71 (35.6%) have been found positive. Among enrolled patients (N = 71), median age was 75 y, 35 (49.3%) had visceral disease, and 22 (31.0%) had ECOG-PS = 2; 50 (70.4%) had CrCl $<$ 60 mL/min and 9 (12.7%) progressed within 6-mos from the end of neo/adj chemo. At the cut-off data (Oct 7, 2021), median follow up was 9.0 mo and 13 patients are still on treatment. The median OS was 10.0 mos (95% CI, 5.7-14.3), and 40.8% of patients were alive at 1-year. The ORR for all patients was 22.5%; complete response, 1.4% (n = 1); partial response, 21.1% (n = 15). Clinical benefit was 43.6% (n = 31). Median PFS was 2.0 mos (95% CI, 1.4-2.6). Among the 56 pts who received at least 3 cycles (29 days) of therapy the median OS was 16.0 vs 1.0 mos. Five (7.0%) grade 3 ave-related adverse events, and no treatment-related death were reported. **Conclusions:** Ave is active and safe in pts with cis-unfit, PD-L1+ve aUC and poor baseline characteristics. Clinical trial information: NCT03891238. Research Sponsor: Alliance Merck-Pfizer.

Final results of a multicenter prospective phase II clinical trial of gemcitabine and cisplatin as neoadjuvant chemotherapy in patients with high-grade upper tract urothelial carcinoma.

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Background: Neoadjuvant chemotherapy (NAC) has proven survival benefits for invasive urothelial carcinoma of the bladder, yet its role in upper tract urothelial carcinoma (UTUC) remains undefined. We conducted a phase II multicenter trial of NAC with gemcitabine and cisplatin (GC) in patients with high-risk UTUC prior to extirpative surgery to evaluate major outcomes of response, survival, and tolerability. **Methods:** Eligible patients with defined criteria for high-risk localized UTUC received four cycles of GC prior to surgical resection and lymph node dissection. The primary study endpoint was pathologic response rate (defined as $<$ pT2N0). Patients with progressive disease prior or unable to proceed to surgery were considered treatment failures. Secondary endpoints included time to disease progression (PFS), overall survival (OS), and safety and tolerability. **Results:** Among 57 patients evaluated, 36 (63%) demonstrated pathologic response, meeting the primary endpoint of the study. A complete response was noted in 11 patients (19%), defined as pT0N0. Forty patients (70%) tolerated all four cycles of GC, and all patients proceeded to surgery. The 90-day $\geq$ grade 3 surgical complication rate was 7.0%. With a median follow up of 42.3 months among survivors, six patients succumbed to disease. Two and five-year PFS were 76% (95% CI 66, 89) and 61% (95% CI 47, 78). Two and five-year OS were 93% (95% CI 86, 100) and 79% (95% CI 67, 94). Patients demonstrating pathologic response had improved PFS and OS compared to those who did not (two-year PFS 91% vs 52%, log-rank $p < 0.001$, two-year OS 100% vs 80%, log-rank $p < 0.001$). **Conclusions:** NAC for high-risk UTUC demonstrates outcomes of favorable pathologic response, is well tolerated requiring minimal delay to surgery without significant perioperative complication risk, and thus should be considered a new standard of care option for patients with high-risk UTUC. Better survival outcomes in patients with favorable pathologic features after NAC indicate a potential clinical benefit to this approach. Clinical trial information: NCT01261728. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Sidney Kimmel Center for Prostate and Urologic Cancers.

Tailored immunotherapy approach with nivolumab in advanced transitional cell carcinoma (TITAN-TCC).

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Background: Nivolumab (nivo) is an approved 2nd line treatment after platinum-based chemotherapy in metastatic urothelial carcinoma (mUC). Recent studies suggest improved outcomes for dual checkpoint inhibition in mUC in particular with higher ipilimumab (ipi) doses (nivo 1mg/kg + ipi 3mg/kg). TITAN-TCC uses a response-based approach starting with 4 doses of nivo (8 weeks) followed by nivo+ipi boosts in non-responders. Here we report cohort 2 of TITAN-TCC applying nivo1/ipi3 boost doses in patients after prior platinum-based chemotherapy (2nd/3rd line). **Methods:** Between April 2019 and February 2021 83 patients with histologically confirmed mUC (TITAN-TCC cohort 2) started with nivo 240mg Q2W induction. After 4 doses and tumor assessment at week 8 (i) non-responders (stable (SD)/ progressive disease (PD)) received 2-4 doses nivo1+ipi3 while (ii) responders (complete (CR)/ partial response (PR)) continued with nivo maintenance but could receive nivo1+ipi3 for later PD. Primary endpoint was confirmed investigator-assessed ORR per RECIST1.1. Using a Fleming single-stage phase II design 77 evaluable patients would provide a 90% power to reject the null-hypothesis that ORR was ≤20% at a one-sided 5% type I error if the true ORR was ≥35%. Secondary endpoints included activity of nivo monotherapy at week 8, remission rate with nivo+ipi boosts, progression-free survival (PFS), overall survival (OS), and safety. **Results:** Median follow-up time was 5.6 months. Of the patients, 78 (94%) were 2nd line. Median age was 68 years (range 37-84) and 57 patients (69%) were male. ORR with nivo monotherapy at first assessment (week 8) was 20.5%. Of the patients, 44 and 6 received nivo+ipi boosts after week 8 and for later PD, respectively. Confirmed objective response with nivo induction ± nivo+ipi boosts was achieved in 27/83 (32.5%) of the patients (significant $> 20\%$, $p < 0.01$). Patients with PD-L1 expression in ≥1% of tumor cells had a numerically higher ORR (46% vs. 24% for PD-L1 negatives). Of the patients with initial SD after nivo induction, 4/13 (31%) achieved response upon boost. Of the patients boosted for PD, 9/37 (24%) improved. Median PFS was 1.9 months (95% CI 1.8-3.2), median OS was 7.6 months (95% CI 5.1-14.9). No new safety signals emerged. **Conclusions:** In patients after prior platinum-based chemotherapy treatment with nivo and nivo+ipi boosts in non-responders significantly improved ORR compared to the one reported for nivo as 2nd line monotherapy. Patients with PD-L1 positive tumors appear to benefit most. Our study provides further evidence for the added value of high dose (3mg/kg) ipilimumab in mUC. Clinical trial information: NCT0321977. Research Sponsor: Bristol Myers Squibb.

n (%)	Nivo mono*	Nivo ± Nivo+Ipi
Objective response rate (best overall response)	17 (20.5)	27 (32.5)
Complete response	2 (2.4)	6 (7.2)
Partial response	15 (18)	21 (25)
Stable disease	11 (13)	8 (9.6)
Progressive disease	51 (61)	46 (55)
Not evaluable/ not assessed	4 (4.8)	2 (2.4)

N = 83; * in first tumor assessment.

Randomized phase II study of niraparib plus best supportive care (BSC) versus BSC alone as maintenance treatment in patients with advanced urothelial carcinoma (UC) whose disease did not progress after first-line platinum-based chemotherapy (PBCT): The Meet-URO12 trial.

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Background: Niraparib is an oral inhibitor of poly ADP-ribose polymerase (PARP) enzymes. Based on the association of mutations in homologous recombination repair (HRR) genes with platinum sensitivity, aim of this phase II trial was to compare maintenance treatment with niraparib plus BSC vs. BSC alone in pts with advanced UC who obtain objective response (OR) or stable disease (SD) with first-line PBCT. **Methods:** Meet-URO12 is a randomized phase II multicentre trial enrolling pts with advanced transitional cell UC, without evidence of progression after 4-6 cycles of first-line PBCT (cisplatin or carboplatin). Pts were randomized (2:1) to experimental arm A (niraparib 300 or 200 mg daily according to body weight and baseline platelets, plus BSC) or control arm B (BSC alone). Primary endpoint was progression-free survival (PFS). 77 pts were planned and 65 PFS events were needed to detect Hazard Ratio 0.57, with 80% power and one-tailed alpha 0.1. Accrual was prematurely stopped due to availability of avelumab in the same setting, and protocol was amended to perform analysis with ≥ 40 PFS events. Molecular characteristics, including alteration of HRR genes, were assessed in formalin-fixed paraffin-embedded tumour samples using the FoundationOne CDx assay. **Results:** Between Aug 2019 and Mar 2021, 58 pts were randomized in 14 Italian centers (39 assigned to arm A and 19 to arm B); 1 pt assigned to arm A did never start niraparib. Median age was 69y (44-84); ECOG PS0 65.5%/ PS1 34.5%; best response with PBCT OR 55.2%/ SD 44.8%. As of Aug 2021, after a median follow-up of 8.5 mos, 47 PFS events were recorded. Median PFS was 2.1 mos in arm A and 2.4 mos in arm B (HR 0.92; 95%CI 0.49 – 1.75, p=0.81). 6-months progression-free rate was 28.2% and 26.3%, respectively. Time to treatment failure for pts who started niraparib was 2.4 mos. Out of 47 pts with molecular info, 21 (44.7%) had HRR alterations: 6 (12.8%) known pathogenic mutations and 15 (31.9%) variants of unknown significance. In pts with pathogenic mutations, median PFS was 2.0 mos in arm A and 1.9 mos in arm B. In pts with any HRR mutation, median PFS was 2.0 mos in arm A and 2.0 mos in arm B. Any grade≥3 treatment-emergent adverse event (AE) was reported in 25/38 pts (65.8%) in arm A and in 3/19 pts (15.8%) in arm B. 18/38 pts (47.4%) needed dose reduction of niraparib. Most common AEs with niraparib were anemia (50.0%, G3 10.5%), thrombocytopenia (36.8%, G3-4 15.8%), neutropenia (21.1%, G3 5.3%), fatigue (31.6%, G3 15.8%), constipation (31.6%, G3 2.6%), mucositis (13.2%, G3 2.6%), nausea (13.2%, G3 2.6%). **Conclusions:** Maintenance niraparib plus BSC did not prolong PFS, as compared with BSC alone, among pts with urothelial cancer without progression after first-line PBCT. Clinicaltrials.gov Identifier. NCT03945084. Clinical trial information: NCT03945084. Research Sponsor: The study was supported by Tesaro - GlaxoSmithKline with experimental drug and research grant.

443 **Poster Session**

E-cigarette use and the risk of bladder and lung cancer.

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Background: Electronic cigarette smoking and similar novel smoking modalities have raised questions about their impact on various cancers compared with traditional forms of tobacco smoking. Tobacco smoking has been concretely proven to increase the risk of many cancers, including lung (LCa) and bladder (BCa) cancer. To date, there is little data on how e-cigarette smoking impacts the incidence of these cancers. We investigated whether any disparities exist in the prevalence of LCa and BCa between various smoking histories using a US nationally representative data source. **Methods:** This cross-sectional survey-based US study included men and women aged 18+ from the National Health Interview Survey (NHIS) database between 2016-2018. Primary endpoint was self-reported occurrence of LCa and BCa diagnosis. Multivariable logistic regression analyses assessed possible association of various covariates with diagnosis of these cancers. **Results:** Prevalence of BCa and LCa was higher in all smoking histories compared to never smokers. Patients with a history of e-cigarette smoking vs. no history of e-cigarette smoking were significantly younger at BCa diagnosis (56.87 [±9.86] vs. 65.00 [±12.60] years, p=0.001). Multivariable logistic regression models showed that a history of cigarette smoking and e-cigarette smoking individually was associated with increased ORs of 2.476 ($p \leq 0.001$) and 1.577 ($p \leq 0.001$) for BCa diagnosis, respectively, and 4.589 ($p \leq 0.001$) and 1.614 (p=0.007) for LCa diagnosis, respectively. **Conclusions:** Compared to never smokers, history of e-cigarette smoking was associated with increased risk of LCa and BCa development and earlier BCa diagnosis. Additional studies are needed to better define the public health effects of these novel and unregulated products. Research Sponsor: None.

Association of household net worth with healthcare utilization in 90-day window after radical cystectomy using real-world data.

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Background: Radical cystectomy (RC) remains the gold standard for muscle invasive bladder cancer yet confers significant healthcare costs. Prior work on the impact of costs commonly relied on comparisons by insurance status (yes/no) and income, a partial proxy for net worth, ie one's net economic standing or value of financial assets minus liabilities. Few have examined the relationship between net worth and encounter type. **Methods:** We identified commercially insured Black, White, Asian, and Hispanic patients who underwent radical cystectomy between January 1, 2007 to April 10, 2021 in The OptumLabs Data Warehouse, a longitudinal, real-world data asset with de-identified administrative claims and electronic health record data. Demographics and costs included household net worth, health plan costs, out of pocket costs, and total healthcare costs accrued from index admission to 90 days after. Multivariable logistic regression models were generated for each encounter type [acute inpatient, emergency department (ED), outpatient, and office visit]. Odds ratios (OR) are presented with 95% confidence intervals (CI) and p-values. A p value of <0.05 was deemed statistically significant. **Results:** The study cohort was comprised of 141,903 patients (2.4% were Black, 11.4% Hispanic, and 8.1% Asian). Household net worth categories were near evenly distributed amongst the study cohort. Acute inpatient encounters harbored the greatest health plan (mean $24,642.80, SD $57,218.41) and out of pocket costs (mean $1,428.24, SD $2108). Office visits conferred the lowest health plan costs (mean $1,126.78, SD $4,119.12) while ED visits had the lowest out of pocket costs (mean $181.88; SD $399.65). Black patients harbored increased odds of an acute inpatient encounter (HR 1.22, 95% CI 1.16-1.29) and ED encounter (HR 1.20, 95% CI 1.14-1.27) while Asian (HR 0.76, 95% CI 0.69-0.85, $p<0.001$) and Hispanic (HR 0.74, 95% CI 0.69-0.78, $p<0.001$) patients had lower odds of an outpatient encounter. Increasing household net worth was associated with decreasing odds of acute inpatient or ED encounters, and greater odds of an office visit. **Conclusions:** Our study is the largest cohort of commercially insured patients to examine variations in healthcare utilization by net worth in the 90 days after radical cystectomy. Those with lower net worth harbored greater risk of an acute inpatient encounter (and higher medical costs) while those with the greater net worth had greater odds of office visits (and lower costs). Greater financial flexibility (i.e., net worth) continues to confer differences in healthcare utilization (and lower healthcare costs), even within a commercially insured population. Household net worth provides a more comprehensive assessment of patients' financial flexibility than income alone and functions as proxy for healthcare access and privilege that could not be directly measured. Research Sponsor: None.

445 **Poster Session**

Longitudinal analysis of bladder cancer-specific mortality trends in the United States.

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Background: Bladder cancer is the most common malignancy of the urinary system. Advances in diagnosis, imaging, and treatments have led to improvements in bladder cancer management. Recent data demonstrate decreasing bladder cancer-specific mortality (BCSM) rates between 2014-2018 for both males and females, however, these trends have not been further examined by race, ethnicity, or geographical location. Using a comprehensive dataset of BCSM over 2 decades, we sought to evaluate differences in BCSM rates overall and by sex, race, ethnicity, location and urbanization category in the United States (US). **Methods:** Age-adjusted mortality rates for bladder cancer (ICD10 code 67) were obtained for males and females of all ages in the US from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database. BCSM rates from 1999-2019 were estimated using linear regression. BSCM trends were evaluated by sex, race (White vs. Black), ethnicity (Hispanic vs. Non-Hispanic), urbanization category, and census region. BCSM rates were compared by F-test. Data analysis was performed using SAS 9.4. All p-values are based on a two-sided hypothesis test with values < 0.05 considered statistically significant. **Results:** From 1999-2019, age-adjusted BCSM rate overall has decreased linearly by (-)0.0073 per 100,000 population/year ($p < 0.05$). Evaluating by sex, both female [(-)0.131] and male [(-)0.022] BCSM rates decreased yearly ($p < 0.05$). By ethnicity, male Hispanic and female Non-Hispanic patients had significantly decreasing BCSM rates [(-)0.021 and (-)0.011, respectively, $p < 0.05$]. White patients had a slightly decreasing rate of BCSM [(-)0.0003, p = NS] while Black patients had an increasing BCSM rate [(+)0.022, $p < 0.05$] – the difference between the two rates was significant ($p < 0.0001$). BCSM rates were significantly decreasing in all census regions (Northeast, Midwest, South, Midwest, $p < 0.05$). BCSM rate in micropolitan (rural) regions has increased yearly [(+)0.006], and rate differences between rural vs large fringe metro (suburban) and vs small metro (population $< 250,000$) categories, both with significantly decreasing BCSM rates, were statistically significant ($p = 0.03$ and $p = 0.047$, respectively). **Conclusions:** Using comprehensive data on BCSM in the United States over two decades, we demonstrate that the overall mortality rate from bladder cancer has been decreasing. However, when disaggregating age-adjusted BCSM by sex, race, ethnicity, census regions, and urbanization categories, significant differences in mortality rates are found including worsening mortality for Black patients, demonstrating that improvements in BCSM are not equitable across variables. Further evaluation of these trends is important to understand how to target specific populations to improve BCSM and overall outcomes for all patients with bladder cancer. Research Sponsor: None.

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Evaluating therapeutic bladder cancer trial disparities in race/ethnicity.

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Background: Racial clinical trial disparities in bladder cancer outcomes remains a critical problem in the United States. This study sought to examine representation by race and sex among therapeutic bladder cancer clinical trials that informs the standard of care in bladder cancer management. **Methods:** Published clinical trial data that inform clinical management were identified from the National Comprehensive Cancer Network guidelines and by clinician input from 2009 to 2021. The characteristics of participants, including sex and race, were collected. Clinical trials were categorized by clinical setting: metastatic bladder cancer (MBC), muscle invasive bladder cancer (MIBC), and non-muscle invasive (NMIBC). Bladder cancer incidence by race were collected from the Surveillance, Epidemiology, and End Results (SEER) Program. SEER incidence data by race was compared to the racial/ethnic breakdown of bladder cancer clinical trial participants and evaluated using hypothesis testing (chi-square). **Results:** A total of 28 clinical trials were assessed, with a pooled sample of 8003 participants. race was reported for 1786 participants. A total of 17 clinical trials did not report race. The population data from SEER details bladder cancer distributions as 89.52% White, 5.80% Black, 0.33% American Indian/Alaska Native, and 4.36% Asian or Pacific Islander. Chi-square analysis demonstrated significant differences in racial representation for MBC ($p < 0.0001$) and NMIBC ($p=0.0423$) settings. No significant differences were observed in the MIBC ($p= 0.1954$) setting. **Conclusions:** This study observed that the distributions of race in MBC and NMIBC clinical trials are different from that of the population affected by bladder cancer. It is imperative for therapeutic cancer clinical trials to achieve adequate representation to ensure standard of care therapies in bladder cancer management benefits all. Research Sponsor: None.

	Metastatic (All) N = 14	Metastatic (Phase I, I/II) N = 9	Metastatic (Phase II/III, III) N = 5	Muscle Invasive (All) N = 9	Muscle Invasive (Phase I, I/II) N = 5	Muscle Invasive (Phase II/III, III) N = 4	Non-Muscle Invasive (All) N = 5	Non-Muscle Invasive (Phase I, I/II) N = 2	Non-Muscle Invasive (Phase II/III, III) N = 3
Total Participants	3726	1345	2381	2047	396	1651	2230	573	1657
Race	N = 1163	N = 758	N = 405	N = 170	N = 170	N = 0	N = 453	N = 453	N = 0
NH White	1033 (89%)	639 (84%)	394 (97%)	154 (91%)	154 (91%)	0	414 (91%)	414 (91%)	0
NH Black	31 (3%)	31 (4%)	0	11 (6%)	11 (6%)	0	15 (3%)	15 (3%)	0
Asian	29 (2%)	29 (4%)		2 (1%)	2 (1%)	0	12 (3%)	12 (3%)	0
American Indian or Alaska Native	0	0	0	0	0	0	2 (≈0%)	2 (≈0%)	0
Native Hawaiian /Other Pacific Islander	3(≈ 0%)	3 (1%)	0	0	0	0	0	0	0
Hispanic or Latino	0	0	0	3 (2%)	3 (2%)	0	0	0	0
Other/Not reported	44 (4%), 23 (2%)	33 (4%), 23 (3%)	11 (3%)	0	0	0	1 (≈0%) 9 (2%)	1 (≈0%) 9 (2%)	0

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Identification of muscle-invasion status in bladder cancer patients using natural language processing and machine learning.

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Background: Mortality from bladder cancer (BC) increases exponentially once it invades the muscle. At the population level, accurate delineation of these patients is challenging. **Methods:** To develop and validate a natural language processing (NLP) model for automatically identifying muscle-invasive BC (MIBC) patients, aiding in population-based BC research. All patients with a CPT code for transurethral resection of bladder tumor (TURBT) (N = 76,060) were selected from the Department of Veterans Affairs (VA) Corporate Data Warehouse database. A sample of 600 patients (with 2,337 full-text notes) who had TURBT and confirmed pathology results were selected for NLP model development (500 patients) and validation (100 patients). Muscle-invasion (yes/no), unknown, or no cancer, were confirmed by detailed chart review of pathology notes. The NLP performance was assessed by calculating the sensitivity, positive predictive value (PPV), and overall accuracy at the individual note and patient levels. **Results:** In the validation cohort, the NLP model had overall accuracy of 88% and 92% at the note and patient levels. Specifically, PPV and specificity for predicting muscle-invasion on note level were 83% and 70%, respectively. The model classified non-muscle invasive BC (NMIBC) with 98% sensitivity at both the note and patient levels. Although the sensitivity for MIBC was 70% for note-level determination, the sensitivity was 86% when evaluated at the patient level. When applying the model to 71,200 patients VA-wide, the model classified 13,642 (19%) as having MIBC and 47,595 (66%) as NMIBC. The NLP model was able to identify invasion status for 96% TURBT patients at the population level. Inherent limitations include relatively small training set given the size of the VA population. **Conclusions:** This NLP model for identifying muscle-invasion at the population level had high accuracy. The NLP model may be a practical and accurate tool for efficiently identifying BC invasion status and may potentially aid in population-based BC research in the VA. Research Sponsor: Department of Defense Peer Reviewed Cancer Research Program (PRCRP) Career Development Award.

Molecular residual disease (MRD) detection with a tissue comprehensive genomic profiling (CGP)-informed personalized monitoring assay: An exploratory analysis of the IMvigor-010 observation arm.

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Background: There is compelling rationale that detection of MRD following curative therapy may identify patients at high risk of relapse requiring intensified adjuvant therapy. Combining MRD detection with CGP creates an opportunity to offer MRD-guided treatment with precision cancer therapeutics. Here we analyze the observation arm of the IMvigor-010 study to understand the genomics of resected early stage bladder cancer and to validate CGP-informed personalized MRD detection in circulating tumor DNA (ctDNA). **Methods:** Using the resected tumor, tissue CGP was performed retrospectively with a 300+ gene assay, followed by MRD detection using FoundationOne Tracker (F1T). Briefly, coding, synonymous, and non-coding variants were selected from tumor tissue sequencing using an optimized algorithm that filters out non-tumor derived variants (germline, clonal hematopoiesis derived, sequencing artifacts). Tumor-informed personalized multiplex PCR-next generation sequencing (Natera) assay was designed and used to detect and quantify variant allelic frequency (VAF) in ctDNA from 182 patients. ctDNA levels were reported in mean tumor molecules per mL of plasma. F1T, a tissue-informed personalized monitoring assay, was performed on plasma samples collected at an MRD timepoint a median of 11 weeks post-surgery. **Results:** At the MRD timepoint, ctDNA was detected in 66/182 (36%). Focusing on the 66 ctDNA-positive patients, 58 had relapsed (88% PPV) at time of analysis. Median disease-free survival (DFS) from randomization was 3 months in ctDNA-positive vs not reached in ctDNA-negative population (HR = 5.7, 95% CI: 3.8-8.6, $p < .0001$). Median overall survival (OS) was 13 months in ctDNA-positive vs not reached in ctDNA-negative (HR = 5.7, 95% CI: 3.4-9.7, $p < .0001$). Potentially actionable CGP findings included *FGFR2/3* short variants (SVs) and fusions (13%), *ERBB2* SVs and amplifications (13%), *PIK3CA* SVs (20%), *CDKN2A* SVs and losses (41%) and tumor mutational burden (TMB) $\geq$10 mutations/Mb (35%). **Conclusions:** Tissue CGP-informed personalized MRD detection can detect low levels of residual ctDNA in patients with resected early stage bladder cancer, identifying a population with inferior DFS and OS. This technologic approach, synergizing regulatory-grade actionable CGP with ctDNA-based MRD detection, creates new opportunities for precision adjuvant therapy across a range of high-risk cancer types. Clinical trial information: NCT02450331. Research Sponsor: Foundation Medicine, Inc.

Early changes in peripheral blood neutrophil-lymphocyte ratio (NLR) to predict outcomes with immune checkpoint inhibitors (ICIs) for metastatic urothelial carcinoma (mUC).

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Background: ICIs have provided advances in the therapy of mUC. However, the objective determination of benefit from ICIs determined by radiographic imaging may take months and may be confounded by pseudoprogression. Peripheral blood cells appear to reflect tumor microenvironment immune infiltrating cells. Given the known prognostic impact of baseline peripheral blood NLR, we aimed to investigate dynamic early changes in NLR as a biomarker of benefit in patients (pts) with mUC. **Methods:** Deidentified data from mUC pts who were treated with ICIs at Dana Farber Cancer Institute from 2015 to 2020 were reviewed retrospectively. Demographic data (age, gender), setting (untreated vs. post-platinum), sites of metastasis, performance status (PS), platelet count, and NLR at baseline and 3-4 weeks after initiating the ICI were collected. We assessed the association of NLR at baseline and 3-4 weeks after starting the ICI with any regression of tumor (ART) and overall survival (OS). A multivariable logistic regression model and Cox proportional-hazards model was employed to identify the association of NLR changes with ART and OS, respectively, using backward selection. **Results:** A total of 144 pts were included. The median age was 76 years and 100 (69.3%) were male. Overall, 54.8% (n=79) had ART and the median OS was 15.2 (12.2-23.5) months. 37.5% (n=54) were platinum naive and the remaining received post-platinum ICI therapy. In the multivariable models (Table), an increase in NLR, defined as an increase in NLR by ≥1.0 from baseline at 3-4 weeks was significantly associated with lower odds of ART (Odds Ratio (OR)= 0.80; 95% CI = 0.70-0.90; p = 0.0004) and worse OS (HR = 1.08; 95% CI = 1.05-1.11; p < 0.0001). The presence of liver metastasis was associated with lower odds of ART (OR = 0.30; 95% CI = 0.13-0.70; p = 0.006) and OS (HR 2.73; 95% CI 1.71 - 4.36; p<0.0001). **Conclusions:** Change in NLR in the first 4 weeks after initiating ICI for mUC was associated with tumor regression and survival in pts with mUC. Change in NLR may assist in early identification of benefit as well as identification of pts who may have progression of disease. Further validation is warranted to facilitate the early discrimination of benefit from ICIs in pts with mUC. Research Sponsor: None.

	ART		OS	
	OR (95% CI)	P-value	HR (95% CI)	P-value
NLR increase by ≥1 at 3-4 weeks	0.80 (0.70 - 0.90)	0.0004	1.08 (1.05 - 1.11)	<0.0001
Liver metastasis	0.30 (0.13 - 0.70)	0.006	2.73 (1.71 - 4.36)	<0.0001

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Comprehensive genomic profiling of urine DNA for urothelial carcinoma detection and risk prediction.

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Background: Clinical diagnosis and risk stratification of patients with urothelial carcinoma (UC) remains a challenge, with high rates of recurrence and disease progression following treatment. Urinary comprehensive genomic profiling (uCGP) has significant potential to aid in both diagnosis and prognostication of non-muscle-invasive and muscle-invasive disease. **Methods:** uCGP was performed on urine specimens collected at 9 centers across the US from 577 subjects prior to cystoscopy. 152 subjects were UC tumor positive (de novo and recurrence), 191 had a history of UC but negative by surveillance cystoscopy at time of collection, and 234 were urology control subjects undergoing cystoscopy without evidence of UC. Urine DNA was sequenced and comprehensively profiled across 60 genes for 6 classes of mutations using the CLIA-validated UroAmplitude test. Disease detection and molecular grade (high grade vs. low grade) algorithms were trained (n=345) and validated (n=232) in independent cohorts. **Results:** Among UC tumor positives, grade distribution was 53% high grade, 41% low grade, and 6% unknown. Stage distribution was Tis (5%), Ta (57%), T1 (16%), ≥T2 (15%), Tx (7%). 99% of tumor positive patients had one or more mutation identified. Interestingly, 69% of UC surveillance negative and 49% of urology controls also had at least one high impact mutation. The prevalence of mutations among controls necessitates machine learning algorithms to classify disease status. In validation, de novo tumor diagnosis demonstrated sensitivity of 93.8% and specificity of 89.4% and a NPV of 98.8% in urology controls. Recurrent tumors were detected with a PPV of 73.5%, sensitivity of 62.5% and specificity of 89.0% in patients with a history of UC. Molecular grading predicted high-grade with a PPV of 90.9% and a specificity of 96.7% compared to pathology. Urinary TP53 mutations were enriched in ≥T2 tumors relative to Ta (OR=14.8 [95%CI 4.6-47.5], P=0.00001). Copy number alterations were also associated with increased risk of muscle invasion, metastasis, and enriched for CIS relative to Ta tumors (≥T2: OR=6.4 [95%CI 1.8-22.9], P=0.019; CIS: OR=10.5 [95%CI 1.9-58.9], P=0.04). **Conclusions:** We developed and validated a uCGP test that provides robust noninvasive detection of UC across a diverse group of patients and clinical contexts, including non-muscle-invasive and muscle-invasive UC. Mutations with actionable or prognostic value are found in most subjects. These data suggest that uCGP classifies tumor presence with better performance than traditional urinary biomarkers. Importantly, uCGP identifies genomic markers of muscle invasion, metastasis, and CIS. With longer term follow-up, uCGP mutational profiles may reveal important prognostic information regarding risk of disease recurrence and progression. Additional studies are underway to further support the generalizability of these findings. Research Sponsor: Convergent Genomics, U.S. National Institutes of Health.

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Inherited germline variants in urothelial cancer: A multicenter whole-exome sequencing analysis.

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Background: Outside of Lynch syndrome, few genetic factors have been associated with urothelial cancer (UC). This project seeks to describe the frequency of germline variants in a multi-center UC cohort. **Methods:** Patients diagnosed with UC from 1980 to 2019 and consented to the Total Cancer Care protocol by members of the Oncology Research Information Exchange Network (ORIEN) were included in the study. The ORIEN program includes a convenience sample of cases with both germline and tumor samples available, though this analysis was germline only. Whole exome sequencing data were analyzed using a GATK best practices for germline variant analysis. A series of quality control (allele frequency $>=$ 0.3, read depth $>=$ 20, genotype quality $>=$ 20), annotation, functional impact (loss of function/splicing), and region (cancer predisposition genes/pathways) filters were applied to identify variants of significant consequence. **Results:** 348 exomes were evaluated. This identified 60 variants classified as pathogenic/likely pathogenic (P/LP) and 17 novel, high impact variants in genes associated with high, moderate, or recessively inherited cancer risk in 77 individuals (22.1%). 15 (4.5%) had P/LP variants in genes associated with a high or moderate cancer risk, and 10 (3%) of these variants were considered to be clinically actionable with associated with cancer screening, risk reduction or treatment recommendations. The high/moderate risk genes with P/LP variants included *CHEK2* (n = 5), *FANCM* (n = 4), *MSH6* (n = 2) and single cases of *MSH2, BRCA2*, *ERCC3,* and *BRIP1*. The average age of diagnosis in those with and without a high/moderate risk P/LP variant was 67.6 (57-80 yrs) and 68.9 (45-91 yrs). Family history of cancer was reported for 73% of those with a germline LP/PV and 60% of those without, but this trend was not significant (p =.44). **Conclusions:** Individuals with UC have a high frequency of germline variants that warrant further study for association with cancer risk. A smaller, but significant portion also carry germline variants that may be clinically relevant to them and/or family members. Currently UC is not included in genetic testing criteria. This study adds to the growing body of research indicating that diverse types of cancer patients harbor germline variants. Strategies for expanding testing should be considered. Research Sponsor: Huntsman Cancer Institute and Oncology Research Information Exchange Network.

The association of FDG PET/CT and NaF PET/CT with survival outcomes in patients (pts) with metastatic genitourinary malignancies (mGU) treated with cabozantinib + nivolumab +/- ipilimumab (CaboNivo +/- Ipi).

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Background: This study determined the association of functional imaging parameters obtained on FDG PET/CT and NaF PET/CT with OS for pts with mGU malignancies treated on a phase I study with CaboNivo +/- Ipi. **Methods:** Pts on this phase I study underwent sequential (1-hour apart) FDG PET/CT and NaF PET/CT imaging at baseline and at first-restaging (8 weeks follow up). Scan semi-quantitative parameters measures included: maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) for FDG and MTV for NaF. Total lesion number was captured for all scans. The association of imaging parameters and survival was determined with Kaplan-Meier curves. Baseline values and percent change values were calculated. **Results:** 81 pts were included in the analysis. 67 (83%) were males; Median age was 63 (range 25-86); Histologically, 30 pts had urothelial carcinoma, 15 clear cell renal cell carcinoma, 9 germ cell tumors, 8 urachal/adenocarcinoma, 8 prostate cancer, 3 penile cancer, 3 squamous cell carcinoma, 3 renal medullary carcinoma, and 2 small cell (1 bladder, 1 prostate). All 81 had a baseline FDG PET scan, 78 pts received baseline NaF PET scans; 66 received both FDG PET and NaF PET baseline and follow up scans. 957 total lesions were detected on FDG PET across all histologies, 87 liver (9%), 252 lung (26%), 152 bone (16%), 411 lymph node (43%), and 55 other visceral metastases (6%). 414 total lesions were detected on NaF imaging. Low vs high baseline FDG MTV (31 vs 11 months, p = 0.0002), TLG (30 vs 11 months, p = 0.0004), Lesion number (49 vs 15 months, p = 0.0005), and SUVmax (25 vs 12 months, p = 0.025), FDG lesion number decrease or no change vs increase (24 vs 12 months, p = 0.0068), and low vs high baseline NaF MTV (26 vs 16 months, p = 0.007), and lesion number (26 vs 16 months, p = 0.007) showed the strongest associations with OS. A multivariable Cox analysis demonstrated that baseline FDG MTV (HR = 2.87, 95% CI 1.62-5.08, p = 0.0003) and FDG lesion number percent change (HR = 2.71, 95% CI 1.40-5.24, p = 0.0031) were jointly associated with OS. **Conclusions:** Baseline functional imaging parameters and percent change seen on follow imaging with FDG PET and NaF PET are prognostic in mGU pts treated with CaboNivo +/- ipi. Additional parameters and histologic subsets will be presented. Research Sponsor: U.S. National Institutes of Health.

Vesical Imaging-Reporting and Data System (VI-RADS).

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Background: The VI-RADS has been widely used as diagnostic criteria for MRI to predict muscle-invasive of bladder cancer (MIBC). The aim of this study is to evaluate the diagnostic performance of VI-RADS in our hospital and the clinicopathological features of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) cases to identify possible factors for misdiagnosis. **Methods:** Of the 286 patients who underwent TURBT at our hospital from January 2019 to October 2020, we selected 129 consecutive cases who had performed preoperative enhanced mpMRI and diagnosed as urothelial carcinoma pathologically. We defined VI-RADS score ≥4 as positive for MIBC. The clinicopathological features of TP, FP, TN, and FN groups were retrospectively analyzed and compared. Chi-square test and Mann–Whitney U test were used for the test between the two groups. **Results:** VI-RADS score in MIBC cases were 2 cases for ≤3 and 22 for ≥4, and in non-MIBC cases 91 cases for ≤3 and 14 for ≥4. The diagnostic performance of VI-RADS for MIBC was 92% for sensitivity, 87% for specificity, 61% for positive predictive value, 98% for negative predictive value, 88% for accuracy and the area under the curve (AUC) was 0.89. There were no statistical differences of age and %male cases between TP (22 cases), FP (14), TN (91) and FN (2) groups. Pathological features of the (TP, FP, TN, FN) groups were shown (table). TP had significantly larger tumor size than the other three groups, and higher %G3, %tumor necrosis and %variant+ than FP and TN. FP group had significantly larger tumor size than the TN. **Conclusions:** VI-RADS showed high diagnostic performance in predicting MIBC. Our study showed that larger tumor size was a significant factor for overestimation, suggesting the need for improved accuracy in cases with large tumor size. Research Sponsor: None.

	Total	TP	FP	TN	FN	p-value					
Variable	(n=129)	(n=22)	(n=14)	(n=91)	(n=2)	TP vs. FP	TN vs FN	TP vs FN	TP vs TN	FP vs FN	FP vs TN
Mean age, yr (range)	77(35-97)	76(61-90)	79(35-97)	73	85	0.346	0.1199	0. 3198	0.8904	0. 6321	0.0904
Sex (n)											
Male	29	17	12	73	2						
Female	7	5	2	18	0	0.5261	0.3507	0. 3219	0.7604	0.4489	0.7882
Tumor size n(%)											
< 3cm	18	8	10	86	2						
≥3cm	18	14	4	5	0	0.0378(red)	0.6364	0.0525	<0.0001	0.2649	0.0174
Tumor mean size (mm)	18.1	37.9	24.8	13.5	9	0.0026	0.3655	0.0245	<0.0001	0.0314	0.0002
median (mm)	14	36	22.5	11	9						
Number of tumors											
single	29	20	9	70	2						
Multiple	7	2	5	21	0	0.0792	0.3026	0.5462	0.2365	0.2023	0.6613
Urine cytology n(%)											
≤Class?	21	12	9	71	1						
≥Class?	15	10	5	19	1	0.562	0.6589	0.9018	0.0654	0.7002	0.5819
Histology grade,n(%)											
Low (G1 or G2)	4	0	4	51	0						
High G3	32	22	10	40	2	0.0038	0.0722		<0.0001	0.2649	0.2334
CIS											
(+)	6	4	2	11	1						
(-)	30	18	12	80	1	0.7579	0.1981	0.3352	0.465	0.276	0.8992
Tumor necrosis											
(+)	10	9	1	7	0						
(-)	26	13	13	81	2	0.0183	0.567	0.1586	0.0004	0.5991	0.1331
Invasive uro urothelial carcinoma subtype (Variant)											
(+)	8	8	0	4	0						
(-)	28	14	14	87	2	0.0023	0.6733	0.1908	0.0001		0.0528

Effect of neoadjuvant chemotherapy (NAC) on patient preferences for adjuvant treatment in muscle-invasive urothelial carcinoma (MIUC): A multi-country discrete choice experiment (DCE).

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Background: Patient preference is an important factor in selecting appropriate treatment choices. Although underutilized, the standard of care for MIUC is with NAC, whereas evidence for adjuvant therapy is less clear. With the introduction of novel adjuvant treatments such as immune checkpoint inhibitors, treatment options are expected to expand. This study examines whether preferences for adjuvant therapy is impacted in MIUC patients receiving NAC. **Methods:** A cross-sectional, web-based survey included patients ≥ 18 years old who self-reported being diagnosed with MIUC and underwent radical cystectomy or nephroureterectomy without recurrence. Patients were recruited from the US, UK, Canada, France, and Germany (May–Sep 2021). A DCE using 2 adjuvant treatment profiles included 8 attributes: cancer-free survival, overall survival (OS), hypothyroidism requiring life-long hormone therapy, risk of a serious adverse event (requiring medical intervention/possible hospitalization), nausea, fatigue, diarrhea, and a dosing regimen (frequency of treatment and monitoring); an opt-out option of no treatment was also shown. Patients were grouped according to self-reported receipt of NAC. Descriptive statistics and hierarchical Bayesian logistic model with estimated preference weights were used. Relative importance estimates (mean ± standard error), or how much the attribute ranges accounted for the variation in preferences, were computed for each attribute. Bivariate comparisons used t-tests. **Results:** This interim analysis identified 205 patients (70.7% of target sample; US, n = 99; Germany, n = 60; UK, n = 31; Canada, n = 14; France, n = 1). Of 82 patients (40.0%) receiving NAC, 32.7% were patients > 65 years and 55.1% were male; receipt of NAC did not differ by age (P = 0.248) or sex (P = 0.731). Patients were willing to accept increased risk in toxicities for increased treatment efficacy. Specifically, mean relative importance of treatment attributes showed that difference in median OS (25 months compared to 78 months) was most important (34.6% ± 1.6), although less so for those who did not receive NAC (30.2% ± 2.4 vs 37.5% ± 2.0; P = 0.022). Patients chose an adjuvant treatment option over 'no treatment' 91% of the time, with similar findings by NAC status. **Conclusions:** Preliminary data indicates that receipt of NAC impacts preferences for adjuvant treatment attributes. However, regardless of these attributes, patients still preferred adjuvant treatment over none. These results suggest that providing standard of care NAC does not reduce patient preference for adjuvant therapy; rather, patient preferences for adjuvant treatment attributes vary by treatment history, with implications for improving quality of care and outcomes. Research Sponsor: Bristol Myers Squibb.

Long-term cost comparisons of radical cystectomy versus trimodal therapy for muscle-invasive bladder cancer.

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Background: Earlier studies on the cost of muscle-invasive bladder cancer treatments are limited to short-term periods of cost. Our study objective is to compare the 2- and 5-year costs associated with trimodal therapy (TMT) versus radical cystectomy (RC) benchmarked against costs for patients who received no curative treatment. **Methods:** This cohort study used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Medicare expenditures were summed from inpatient, outpatient, and physician services within 2 and 5 years of diagnosis to determine total costs Total Medicare costs at 2-and 5-years following TMT versus RC were compared using inverse probability of treatment-weighted (IPTW) propensity score models. **Results:** A total of 2,537 patients aged 66-85 years diagnosed with clinical stage T2-4a muscle-invasive bladder cancer from January 1, 2002 through December 31, 2009. Total median costs for patients that received no definitive/systemic treatments (RC, TMT, radiotherapy alone, or chemotherapy alone) were $73,780 vs. $88,275 at 2-and 5-years respectively. Total median costs were significantly higher for TMT than RC at 2-years ($372,839 vs. $191,363, $p<0.001$) and 5-years ($424,570 vs. $253,651, $p<0.001$), respectively. TMT had higher outpatient median costs than RC (2-yr: $318,221 vs. $100,900; 5-yr: $367,092 vs. $146,561) with significantly higher costs largely associated with radiology, medications, pathology/laboratory, and other professional services. **Conclusions:** TMT vs. RC was associated with higher long-term costs among patients with muscle-invasive bladder cancer largely driven by outpatient expenditures. Reduction in costs associated with radiology, medications, pathology/laboratory, and other professional services may improve the value of TMT. Research Sponsor: Department of Defense Peer Reviewed Cancer Research Program (PRCRP) Career Development Award (W81XWH1710576) and the Herzog Foundation.

Medicare Costs (USD) associated with radical cystectomy and trimodal therapy following bladder cancer diagnosis.

	Median, $						
	Radical Cystectomy			Trimodal Therapy			Hodges-Lehmann Estimate (95% CI)
Years	Total	Inpatient	Outpatient	Total	Inpatient	Outpatient	
2	191,363	62,240	100,900	372,839	33,631	318,221	127,815 (112,663-142,966)
5	253,651	75,499	146,561	424,570	45,223	367,092	124,466 (105,711-143,221)

Disease management and frontline treatment of locally advanced or metastatic urothelial (la/mUC) carcinoma: The U.S. physician PARADIGM study.

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Background: The treatment landscape for la/mUC is evolving. Data on current real-world treatment trends in la/mUC are limited. This study assessed US physician treatment decision-making and prescribing patterns using qualitative interviews (QIs). **Methods:** First, a targeted literature search (TLS) evaluated published abstracts from January 2018 to March 2021. Then, in July 2021, QIs with 15 US medical oncologists/urologists were conducted based on the TLS findings. Physicians were recruited for a 60-minute, 1-on-1 phone interview. Physicians had to be in practice ≥1 year post fellowship, a board-certified oncologist/urologist, and managed ≥1 la/mUC patients who received first-line (1L) systemic therapy in the past 6 months. **Results:** Seven published US retrospective studies found relatively low utilization of 1L systemic therapy with 40%-65% of la/mUC patients not treated; high attrition rates reported with only 15%-40% of 1L patients receiving second-line (2L) therapy. The TLS included patient data collected primarily through 2017 and did not capture current systemic treatment patterns for recently approved therapies. QI respondents were community oncologists (n = 8), academic oncologists (n = 4), and community urologists (n = 3). The average number of la/mUC patients seen in the past 6 months was 23 per physician. Physicians estimated that ≥75% la/mUC patients are currently being treated with systemic therapy, with all oncologists prescribing 1L immunotherapy (IO) maintenance to eligible patients (n = 10 prescribing avelumab for ≥90%). According to 11 respondents (73%), the proportion of systemic-treated patients has increased in recent years with the availability of IO and novel therapies. Top reasons for not prescribing systemic therapy were poor performance status (73%), old age (67%), patient preference (53%), and comorbidities (47%). Physician-reported 1L regimens administered were 41% carboplatin-based, 37% cisplatin-based, 17% single-agent IO, and 4% nonplatinum chemotherapy. Top criteria impacting 1L regimen choice were renal function (100%), performance status (75%), neuropathy (75%), and age (50%). IO was typically reserved for patients who were platinum ineligible or refused chemotherapy. Ten oncologists reported that 60%-80% of 1L la/mUC patients received a 2L treatment. **Conclusions:** From the QIs, physicians reported higher treatment rates compared to the TLS; however, our physician sample was small, and the TLS included patient data through 2017 and thus did not capture current systemic treatment patterns. Findings suggest that, over time, the proportion of US la/mUC patients treated with/eligible for 1L systemic therapy has increased, including IO maintenance, as well as for subsequent lines due to increased treatment options after 2017. A quantitative survey of 150 medical oncologists is planned next for this study. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), Pharmaceutical/Biotech Company.

457 **Poster Session**

Criteria used to determine platinum eligibility and first-line (1L) treatment (tx) patterns among platinum-eligible (PE) and -ineligible (PI) patients (pts) with metastatic urothelial cancer (mUC) in France, Germany, Spain, Italy, and the United Kingdom (Eu5).

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Background: European Society for Medical Oncology (ESMO) guidelines recommend tx for mUC based on cisplatin and platinum eligibility. To date, most real-world analyses have not included physician-confirmed eligibility status. This study collected mUC patient data in Eu5 and summarized the criteria used in the real-world setting to determine PE and 1L tx prescribed based on PE. **Methods:** Data were drawn from the Adelphi mUC Disease-Specific Programme, a real-world point-in-time study conducted from November 2020 to April 2021. Oncologists and urologists were enrolled in the study and recruited the next 8 eligible pts who came for a consultation. Demographic, clinical characteristics, platinum eligibility, and tx patterns were collected. **Results:** Physicians provided data on 1,868 mUC pts who were receiving or had completed 1L tx and had a known PE status as determined by a physician prior to 1L tx. Renal function contributed to physicians' platinum eligibility decisions for 72% of pts; ECOG score and age were used in 59% and 38% of pts, respectively. The mean (SD) age was 69.1 (7.88) years and 73% were men. At initial mUC diagnosis (dx), 25% were PD-L1–positive, 17% were PD-L1–negative, and 58% had either unknown PD-L1 status or were not tested. 87% of pts were PE (55% were eligible for cisplatin and carboplatin; 31% were cisplatin ineligible), and 13% were PI. PE pts who were eligible for cisplatin and carboplatin were younger than cisplatin ineligible and PI pts (66.6, 71.9 and 73.1 years, respectively). The percentage of pts with ECOG 0 or 1 at dx was 92%, 79%, and 67% for cisplatin and carboplatin eligible, cisplatin ineligible, and PI pts respectively. **Conclusions:** Only a small proportion of pts were classified as PI. The majority of PE pts received guideline-recommended tx with platinum-based regimens in the 1L. Overall, there was limited use of immune checkpoint inhibitor tx in the 1L, with use observed primarily among PI pts. Some guideline deviations were observed, including pts deemed PI who still received platinum-based chemotherapy. Recently, ESMO guidelines were updated to include avelumab for 1L maintenance tx in PE pts. Future studies should evaluate concordance with updated guideline recommendations in PE pts and rationale for guideline deviations. Research Sponsor: Pfizer, Pharmaceutical/Biotech Company.

	PE		PI
1L regimen received n (%)*	Cisplatin AND carboplatin eligible n=1,036	Cisplatin ineligible BUT carboplatin eligible n=584	Cisplatin AND carboplatin ineligible n=248
1L cisplatin-based regimen, 962 (51)	894 (86)	27 (5)	41 (17)
1L carboplatin-based regimen, 580 (31)	47 (5)	502 (86)	31 (12)
1L immune ICI monotherapy, 190 (10)	51 (5)	37 (6)	102 (41)
1L any chemotherapy (excluding platin-based and ICIs), 101 (5)	26 (3)	9 (2)	66 (27)
Other, 35 (2)	18 (2)	9 (2)	8 (3)

ICI, immune checkpoint inhibitor.

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Response to neoadjuvant chemotherapy in histologic variants of bladder cancer.

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Background: Localized muscle invasive bladder carcinoma is mostly treated with neoadjuvant chemotherapy (NAC) before surgery in order to improve the outcome. Urothelial carcinoma (UC) is the most frequent histological type. Histological variants (pure or mixed) occur in 10% of bladder carcinoma. There is a lack of data on NAC efficacy for these histological subtypes. In this study, we evaluated the histologic response to NAC in the variant population of bladder cancer. **Methods:** Patients from 2 french hospitals (CHU de Nantes and ICM) treated with NAC for bladder cancer from 2010 to August 2021 were included in this retrospective study. We compared response to NAC between UC and histologic variants (pure or mixed) on cystectomy piece. The histological response was defined by the tumor downstaging after NAC (≤pT1Nx). We also collected the pathological complete response (pCR), which was defined by no residual tumor on the cystectomy piece. **Results:** 87 patients were included. 31 patients harbored a variant pattern: 7 squamous component, 3 adenocarcinoma component, 5 micropapillary component, 2 sarcomatoid component, 4 neuroendocrine carcinoma, 4 nest, 1 lymphoepithelial carcinoma, 2 giant cell, 1 undifferentiated, 1 micropapilallary and adenocarcinoma component and 1 adenosquamous component; 56 were conventional UC. NAC was MVAC in 77% of patient in the variant group, and 82% in the UC group. Others chemotherapy drugs were used as gemzar cisplatine, and platine etoposide. Downstaging was observed in 55% of patients in the variant group (17/31) and in 59% in the UC group (33/56). The difference was not statistically significant (p <0,44). pCR was observed in 39% of patients in the variant group (12/31) and 43% in the UC group (24/56), the difference was not significant (p< 0.44). **Conclusions:** NAC can be effective in the histologic variant population of bladder carcinoma, nevertheless these data could be confirmed in a larger cohort. Research Sponsor: None.

459 **Poster Session**

Impact of FDA label change on immunotherapy for metastatic urothelial cancer (mUC) and subsequent changes in mortality.

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Background: In May 2017, atezolizumab and pembrolizumab (IO) received accelerated approval for first-line treatment of cisplatin-ineligible patients with mUC, irrespective of PDL1 test status. In June 2018, the FDA and EMA restricted IO to cisplatin-ineligible patients with PDL1 positive tumors based on early review of data from confirmatory trials which suggested decreased overall survival in patients with PDL1 negative tumors treated with IO. We assessed the impact of the FDA label change on clinical outcomes of mUC patients in routine care. **Methods:** We conducted a controlled interrupted time series analysis using the US Flatiron Health electronic health record-derived de-identified database. The study sample included patients from 280 cancer clinics nationwide diagnosed with mUC and compared patients potentially impacted by the label change (cisplatin ineligible patients initiating first-line IO or carboplatin-based chemotherapy) to a comparator group who would have been unaffected by the label change (patients initiating first-line cisplatin-based chemotherapy) from 01 April 2017 to 17 May 2018 (pre-label change) and 20 June 2018 to 01 March 2020 (post-label change), excluding a 30-day wash out period encompassing the time-period between the initial FDA safety alert (18 May 2018) and the official FDA label change (19 June 2018). We used Cox regression to estimate adjusted pre-/post-label change related mortality differences in patients receiving carboplatin-chemotherapy or IO, accounting for secular changes in survival through comparison with the cisplatin comparator group. **Results:** The study included 829 patients with mUC initiating treatment in the pre-label change period (582 IO or carboplatin, 247 cisplatin) and 1,184 patients in the post-label change period (849 IO or carboplatin, 336 cisplatin), respectively. The use of IO, carboplatin, and cisplatin was similar across time-periods (pre-label change: 44.4%, 25.8%, and 29.8%; post-label change: 48%, 23.6%, 28.4%); while PD-L1 testing increased (6.6% to 28.1%). In adjusted models, there were no differences in survival in any of the groups following the FDA label change policy (table). **Conclusions:** The U.S. FDA label restriction on first-line immunotherapy was associated with increased PD-L1 testing but was not associated with changes in treatment patterns or improved mortality among patients with mUC. Research Sponsor: Merck & Co, Inc.

	Pre- vs post- FDA label change policy			
	Mortality Hazard Ratio (HR) (95% CI)	P	% Difference in 24 mo survival probability	P
Cisplatin	1.03 (0.83 – 1.29)	0.764	-1.2 (-27.3, 25.0)	0.930
Carboplatin or IO	1.02 (0.88 – 1.18)	0.795	-0.7 (-18.6, 17.3)	0.944
Difference-in-differences	0.99 (0.77 – 1.27)*	0.912	0.5 (-13.2, 14.2)	0.942

*Interaction HR, corresponding to the ratio of ratios on the HR scale, an estimate of the multiplicative difference in the pre/post change between treatment groups.

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Impact of COVID-19 on cancer caregivers: Results from the Global Carer Well-being Index.

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Background: Caregiver burden has been intensified by the COVID-19 pandemic. The Carer Well-being Index is a global research study commissioned by Embracing Carers, a partnered initiative with nine global caregiving organizations. The study sought to explore and delineate the impact of the pandemic on the health and well-being of caregivers across the globe, including those caring for persons with cancer. **Methods:** The survey was conducted via online and phone methodologies in September and October 2020, with over 9,000 unpaid carers across 12 countries, including the United States and Canada. Unpaid carers were defined as those who care for someone with a long-term illness (e.g., cancer), physical disability (e.g., spinal cord injury), or cognitive/mental condition (e.g., Alzheimer's). The base sample size for cancer caregivers from the global surveyed population was n=1035. Statistically significant differences between cancer carers and non-cancer carers were evaluated using the Chi-square test with $p \leq 0.05$. **Results:** 63% of all caregivers were women, with a 60/40 female to male split in the cancer carer group. While the average age of started caregiving was 37.2 years, and 39.0 in cancer carers, caregivers caring for someone with cancer were more likely than the average caregiver to be in the 60+ age group. Compared to non-cancer caregivers surveyed, a higher percentage of cancer caregivers became carers in the last year (26 vs 13% of non-cancer caregivers). Providing emotional support, managing doctor appointments, preparing meals, home maintenance and housekeeping, transportation, and giving/managing medications were more likely to be among cancer caregivers' primary responsibilities, compared to non-cancer caregivers. Cancer carers were significantly more likely than non-cancer carers to have reported negative impacts because of COVID on their emotional/mental, physical, and financial health, and paid work responsibilities. Overall, cancer caregivers were significantly more likely to report that COVID has made caregiving harder than non-cancer caregivers (71 vs 63%), and were more likely to report never receiving support from a variety of organizations, such as insurance organizations (71 vs. 66% non-cancer caregivers) and local/state government (73 vs. 66%). Of note, cancer carers were more likely to report a positive impact on the relationship with the person being cared for (61 vs. 56%). **Conclusions:** These results highlight the burdens that have been intensified for cancer carers. Actions are needed to help with health and well-being such as offering and promoting mental health services, respite care; providing financial support to take leaves from paid work, access to equipment and services such as housecleaning. By working together with health care providers, organizations, and government on these types of initiatives, the burden upon cancer caregivers can be lessened. Research Sponsor: EMD Serono (CrossRef Funder ID: 10.13039/100004755).

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Real-world evidence from a single U.K. cancer center for atezolizumab in second-line setting in advanced urothelial cancer: Moving beyond clinical trials.

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Background: Atezolizumab is approved for use in advanced urothelial cancer in second line setting after platinum based chemotherapy. We conducted a retrospective study to evaluate clinical outcomes in patients treated in a single UK cancer centre with Atezolizumab for advanced urothelial cancer. **Methods:** Data was collected from electronic records for patients treated with Atezolizumab for advanced urothelial cancer patients between January 2019 to June 2021. Patients with histologically proven advanced urothelial cancer, PS 0-1, GFR $>$ 30 ml/min by Cockcroft-Gault formula, who had progressed after platinum based chemotherapy were eligible. Maximum duration of treatment allowed was 24 months as per National Cancer Drugs Fund criteria. Initially 3 weekly cycles using Atezolizumab at a dose of 1200 mg was used, patients received 4 weekly dose once 1680 mg dose was available. Kaplan Meier survival estimates were used to calculate progression free survival and overall survival. **Results:** 32 patients received Atezolizumab between Jan 2019 to June 2021. The mean age was 70.6 years (range 44-88). 10 patients had ECOG PS 0, 22 patients had PS 1. Male 19, Female 13. At the time of analysis, 9 out of 32 patients were alive, 2 patients had completed 24 months of treatment and had no evidence of disease progression. Total 297 cycles of Atezolizumab were delivered (190 cycles were delivered at 3 weekly intervals, while 107 were delivered 4 weekly). The median progression free survival was 24.290 weeks (95% CI: 23.202-25.378), and the median overall survival was 40.860 weeks (95% CI: 19.788-61.932). 10 patients (31.2%) were alive at 12 months, 8 patients (25%) were alive at 18 months. The number of patients with toxicity of grade $\geq$3 were 4.There were no treatment related deaths. **Conclusions:** Atezolizumab is effective and well tolerated in patients with advanced urothelial cancer in second line setting. Durable responses were noted with 25% of patients alive at 18 months. Research Sponsor: None.

Impact of selection bias on outcomes in veterans with muscle-invasive bladder cancer receiving bladder preserving trimodality therapy.

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Background: Retrospective studies using large registries comparing outcomes between radical cystectomy (RC) with or without neoadjuvant chemotherapy (NAC) to trimodality therapy (TMT), which includes transurethral resection of bladder tumor followed by chemoradiation, often cannot distinguish whether patients receiving TMT were eligible for cystectomy but declined or simply ineligible for cystectomy. The objective of this study was to compare survival outcomes of patients with MIBC receiving TMT stratified by whether they were cystectomy-eligible to patients receiving RC +/- NAC. **Methods:** We used the national Veterans Affairs' (VA) database to identify patients diagnosed between 2000-2017 with urothelial histology, MIBC (T2-4a/N0-3/M0) who underwent RC or TMT. Overall survival (OS) was evaluated with multivariable Cox proportional hazards model. Bladder cancer-specific mortality (BCSM) was evaluated with multivariable Fine-Gray regression. We conducted a chart review of clinical notes to ascertain if patients were eligible for cystectomy. **Results:** Overall 2306 Veterans with MIBC were included: 1472 (64%) with RC without NAC, 506 (22%) with RC-NAC, 107 (4.6%) with TMT eligible for RC, and 221 (9.4%) with TMT ineligible for RC. Median follow up time was 4.7 years. Patients receiving RC were on average 10 years younger, had higher creatinine clearance, and fewer comorbidities than those receiving TMT. Cystectomy-eligible TMT patients had higher creatinine clearance and fewer comorbidities than those ineligible for cystectomy. On multivariable analysis, compared to RC-NAC, TMT in cystectomy-eligible patients was associated with similar OS (hazard ratio [HR] 0.99; 95% confidence interval [CI] 0.76 - 1.28; $p = 0.93$) and BCSM (HR 1.02; 95% CI 0.71-1.47; $p = 0.91$). Compared to RC-NAC, TMT in cystectomy-ineligible patients was associated with inferior OS (HR 1.39; 95% CI 1.13 - 1.71; $p = 0.002$) and BCSM (HR 1.61; 95% CI 1.23 - 2.10; $p < 0.001$). **Conclusions:** There is a significant selection bias among patients with MIBC receiving TMT. Cystectomy-eligible patients receiving TMT likely have similar survival outcomes as those receiving RC. Comparisons between RC and TMT in large registry data that lack information regarding eligibility for cystectomy in the TMT arm may be unreliable. Research Sponsor: U.S. National Institutes of Health.

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Contemporary treatment and survival differences in patients with urothelial versus nonurothelial bladder and upper tract carcinomas: Analyses from the National Cancer Database (NCDB).

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Background: Non-urothelial bladder and upper tract cancers are known to have worse prognosis than urothelial cancers. Further descriptive analyses of patterns of demographic presentation, stage, metastases and response to chemotherapy and immunotherapy are explored through the NCDB database. **Methods:** The primary objective of this retrospective review is to evaluate trends and differences between upper tract urothelial cancers (UTUC) versus non-urothelial (nUTUC) histologies (squamous, sarcomatoid, small cell or neuroendocrine, adenocarcinoma) and bladder urothelial cancer (UC) and bladder non-urothelial cancer (nUC) and compare the demographics, disease characteristics, treatment, incidence of stage and survival according to NCDB. **Results:** Data from diagnosis in year 2004 – 2017 were extracted from the NCDB. A total of 649939 cases of whom 630423 were urothelial and 19516 were non-urothelial for both bladder and upper tract cancers were identified. More men were diagnosed with urothelial carcinoma, UTUC (62%) and bladder UC (75%). The median age was similar for both groups, 71.4 years (UC) and 70.1 years (nUC). Majority were Caucasian at 91.6% (UC) and 85.7% (nUC) while African-American patients consisted of 5.26% in the UC and 10.8% in the nUC cohorts. Primary surgery occurred more frequently in the UC cohort (94.7%) compared to the nUC (87%). More patients were diagnosed with stage IV cancer in the nUC group (21.9%) compared to UC at 4.6%, and overall survival was slightly worse with nUC for stage IV cancers with median OS of 7.92 mos (CI, (7.75, 8.08) for UC vs 6.14 mos (CI, (5.78, 6.47) nUC; logrank $p = < 0.001$, although the biggest numeric difference was in the stage 0 and stage I patients with mOS of 110.13 mos (CI, 109.44, 110.82) versus 46.09 mos (CI, 42.09, 50.66), $p < 0.001$. Use of chemotherapy resulted in improved overall survival in the UC group with mOS of 73.53 mos (CI, 72.61, 74.41) compared to nUC at 17.28 mos (CI, (16.59, 17.87), $p < 0.0001$ and use of immunotherapy similarly yielded improvement in the UC group with mOS of 115.98 mos (CI, 114.33- 117.65) compared to nUC at 64.49 mos (CI, 45.67, 88.51); $p < 0.0001$. **Conclusions:** Urothelial cancer of both bladder and upper tract origin compared to non-urothelial cancers tend to have better prognosis in both presentation at diagnosis and with early stage cancers as well as treatment in advanced stages with chemotherapy or immunotherapy, highlighting the need for better therapeutic strategies for non-urothelial cancers. Research Sponsor: None.

Management, surveillance patterns, and costs associated with low-grade papillary (Ta) nonmuscle-invasive bladder cancer.

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Background: Low-risk non-muscle invasive bladder cancer (NMIBC) is associated with extremely low rates of progression and cancer-specific mortality, however, these patients may often receive non-guideline recommended and potentially costly surveillance and treatment(s). We sought to describe current surveillance and treatment practices, oncologic outcomes, and cost of care for low-grade papillary (LG Ta) NMIBC and identify predictors of increased cost of care. **Methods:** This population-based cohort study identified 13,054 patients diagnosed with LG Ta tumors in the Surveillance, Epidemiology and End Results-Medicare linked database from January 1, 2004 through December 31, 2013. The primary outcome was to characterize trends in population-level surveillance and treatment practice patterns over time among LG Ta patients. The secondary outcomes were recurrence, progression, and costs of care. **Results:** Of the 13,054 patients who met inclusion criteria, 9,596 (73.5%) were male and 3,485 (26.5%) were female, with a median age of 76 (Interquartile Range (IQR): 71–81) years. Rates of surveillance cystoscopy increased over the study period (79.3% to 81.5%, $p = 0.007$) with patients undergoing a median of three cystoscopies per year (IQR: 2–4). Rates of upper tract imaging utilization also increased, namely the use of computed tomography (CT) or magnetic resonance imaging (MRI) (30.4% to 47%, $p < 0.001$), with most patients undergoing a median of two imaging tests per year. Similarly, the use of urine cytology or other urine biomarkers also increased (44.8% to 54.9%, $p < 0.001$). Rates of compliance with current guidelines decreased over time suggesting overutilization of all surveillance testing modalities. A total of 17.2% of patients received intravesical bacillus-Calmette Guerin (BCG) and 6.1% received intravesical chemotherapy (excluding single perioperative dose). Among all LG Ta patients, 1.7% and 0.4% experienced disease recurrence and progression, respectively. Total annual median costs of LG Ta surveillance and care increased 1.6-fold from $34,792 to $53,986 over the study period, with increased expenditures noted among those with disease recurrence ($53,909 and $76,669). **Conclusions:** Despite low rates of disease recurrence or progression, rates of surveillance testing increased during the study period. Annual cost of care increased over time, particularly among patients with recurrent disease. Efforts to improve adherence to current practice guidelines, with the focus on limiting overutilization of surveillance testing and overtreatment, may mitigate associated rising costs of care. Research Sponsor: Department of Defense Peer Reviewed Cancer Research Program (PRCRP) Career Development Award (W81XWH1710576).

465 **Poster Session**

Regional trends in the cost of transurethral bladder tumor resection in the outpatient and physician office setting.

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Background: TURBT is the standard surgical procedure for diagnosis, staging, and initial treatment of non-muscle invasive bladder cancer. This study aimed to identify current geographic trends associated with the use and cost of TURBT in Medicare beneficiaries. **Methods:** The Medicare Limited Data Set 100% sample of outpatient and 5% sample of carrier claims data from Q1 2019 to Q3 2020 was used for analysis. Patients who underwent TURBT were identified using CPT codes (55234, 52235, 52240). An analysis of variance (ANOVA) test was run comparing the difference in average claim payment amount, average beneficiary payment to physician, and average allowed charge amount between each region (West, Midwest, Northeast, and South). If the ANOVA test found a significant difference between regions, a t-test was run for all combinations of regions. **Results:** In the outpatient setting, we identified a total of 92,938 TURBT procedures between 2019 and Q3 2020, including 23,039 (Midwest), 19,890 (Northeast), 33,379 (South), and 16,630 (West). The average Medicare claim payment amount was $2,755 overall, $2,566 (Midwest), $2,866 (Northeast), $2,497 (South), and $3,092 (West). Beneficiaries paid an average of $605 in the Midwest, $673 in the Northeast, $572 in the South, and $697 in the West. The average total charge was $7,343, $7,189, $8,510, and $10,028 in the Midwest, Northeast, South, and West respectively. In the outpatient setting, there were no statistical differences for any cost related variables between the four regions. In the physician office setting, we identified 8,035 TURBT between 2019 and Q3 2020. There were 1,776, 1,577, 3,153, and 1,529 TURBT procedures in the Midwest, Northeast, South, and West, respectively. The average Medicare claim cost was $383 (Midwest), $372 (Northeast), $423 (South), and $417 (West). The average total allowed charges on the claim was $415 overall, and $392, $404, $430, and $432 in the Midwest, Northeast, South, and West, respectively. There was a significant statistical difference ($p = 0.0154$) for the average claim payment amount between the South and the Northeast. The two regions differed in average claim payment amount by $51 (95% CI: $15, $87). There was a significant difference in the average allowed charge amount between the South and Midwest ($p = 0.019$) and the West and Midwest ($p = 0.016$). Compared to the South, the Midwest had a lower average charge amount by $37 (95% CI: $9, $66). The West had a higher average charge amount than the Midwest by $40 (95% CI: $12, $68). **Conclusions:** This analysis demonstrated a significant difference in the cost of TURBT between regions in the physician office setting. The South had a significant higher claim payment amount than the Northeast. The allowed charge amount in the physician office setting for the South and the West were significantly higher than the Midwest. Research Sponsor: None.

Use of perioperative treatment (tx) among patients (pts) undergoing radical resection (RR) for muscle-invasive urothelial cancer (MIUC) in France, Germany, Italy, Spain, the United Kingdom, the United States, Canada, China, and Japan.

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Background: Cisplatin-based neoadjuvant chemotherapy (NAC) followed by RR is the standard of care in cisplatin-eligible pts with MIUC. Adjuvant chemotherapy (AC) with cisplatin-based tx may be offered to those not given NAC. The unmet need this survey tried to evaluate is the post-RR burden of disease, quality of life (QoL) and perioperative tx patterns among MIUC pts. **Methods:** Real-world descriptive data were drawn from Adelphi's MIUC Disease-Specific Programme: A point-in-time survey conducted with clinical/medical oncologists/urologists and their pts in 9 countries between January and June 2021. Physicians completed a survey on their pts' clinical characteristics and tx patterns, while pts voluntarily completed a series of patient-reported outcome measures. **Results:** Of 2178 pts (data provided by 320 physicians), 30% received NAC only, 26% received AC only, 38% received no NAC or AC tx, and 6% received both. 1744 pts had initial tumour in the bladder; 35% received NAC only, 24% AC only, 35% no NAC or AC tx, and 6% received both. Of 387 pts with upper-tract urothelial carcinoma (UTUC), 51% received no NAC/AC tx, 35% received AC only, and 12% NAC only. More pts with T3 disease received no NAC/AC tx (36%) or NAC (35%) than AC (24%). Of 734 pts with nodal disease, 36% received NAC only. Of all pts, 60% experienced symptoms at data abstraction: 50% in pts who received NAC only, 71% in pts who received AC only and 82% in pts of those who received both. Pts reported similar EQ-5D-5L utility index scores (mean = 0.86; range: 0.84 [AC only] to 0.89 [NAC only]). Overall, feeling pain (40%) and stress (39%) were the EQ-5D domains with the worst scores. Pts who received AC only reported nominally lower EQ-5D visual analogue scale scores (71.11) compared with pts who received no NAC/AC (73.17) or pts who received NAC only (75.05). EORTC QLQ-C30 Global Health Status scores were 60.0 in pts who received AC only, 64.1 in pts who received NAC only or no NAC/AC, and 66.7 for pts who received both NAC and AC. **Conclusions:** Nearly 40% of pts remain untreated in either NAC or AC setting in 9 countries. A higher proportion of pts with UTUC go untreated. AC was more frequently used in UTUC vs BC pts; and in pts with Tis. NAC was implemented more frequently in pts T3 disease and in those with N+ disease. Pts who received AC appear to have nominally worse QOL and more symptoms, further demonstrating the need for efficacious adjuvant tx that does not decrease post-RR QoL. Research Sponsor: Bristol Myers Squibb.

Tx types by T and N stage at initial diagnosis (%).

Stage (Base)	NAC only n=664	AC only n=562	No NAC or AC n=826	Both NAC and AC n=126
Unknown T stage, n=13	0	23	62	15
Tis, n=83	8	34	55	2
T1, n=140	25	19	50	6
T2, n=140	19	23	50	8
T3, n=1181	35	24	36	5
T4, n=493	33	31	28	9
Unknown N stage, n=157	24	31	41	4
N0, n=1159	30	20	44	5
N1, n=734	36	32	25	8

Impact of care fragmentation in patients receiving neoadjuvant chemotherapy and radical cystectomy for bladder cancer.

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Background: Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is the standard of care for muscle-invasive bladder cancer (MIBC). However, the impact of care fragmentation on the outcomes of patients receiving NAC and RC for MIBC is not well defined. **Methods:** The National Cancer Database was queried for adult (≥18 years old) patients with cT2-T4aN0M0 urothelial carcinoma of the bladder receiving NAC followed by RC between 2004 and 2017. Patients were dichotomized based on whether they received fragmented care (FC, defined as receiving NAC at a different facility from RC) or integrated care (IC, defined as receiving NAC and RC at a single facility). Descriptive statistics were used to characterize the two groups based on demographic and therapeutic profiles. Overall survival was compared between patients who received FC versus IC. Statistical analyses include Chi-squared tests, *t*-tests, Kaplan-Meier with log-rank test, and Cox regression analysis. **Results:** A total of 5054 patients received NAC followed by RC: 1848 (36.6%) received FC and 3206 (63.4%) received IC. Greater travel distance, private insurance, and treatment at a community cancer program were associated with FC whereas age, sex, race, median income, education level, rurality, and comorbidity burden were not. While patients who received FC had a longer time to initiation of NAC (40 vs. 37 days, $p< 0.001$), there was no significant difference in median overall survival (OS) (84.3 vs. 92.8 months, $p= 0.37$). On multivariable Cox regression analysis, age, comorbidity burden, stage, lymphovascular invasion, and surgical margins were associated with OS, while FC was not (hazard ratio: 1.03; 95% confidence interval 0.94-1.13; $p= 0.51$). **Conclusions:** Although care fragmentation was associated with a slight delay in the initiation of NAC, long-term survival rates were similar between the FC and IC groups. Research Sponsor: None.

Parameter	Hazard ratio	95% confidence interval	*p*-value
Age	1.03	1.02-1.04	< 0.001
Fragmented care	1.03	0.94-1.13	0.513
Charlson-Deyo score = 2	1.28	1.07-1.54	0.007
NCDB analytic stage group			
Stage II	1.42	1.14-1.76	0.001
Stage III	3.39	2.74-4.20	< 0.001
Stage IV	5.86	4.70-7.31	< 0.001
Lymphovascular invasion present	1.54	1.38- 1.73	< 0.001
Surgical margins = R2	2.14	1.38-3.32	< 0.001

469 **Poster Session**

FGFR testing and urine-based risk straticfication from matched tissue and urine samples within the prospective real-world clinicopathological register trial: BRIDGister.

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Background: The objective of the present study was to assess FGFR mutattions and fusions from matched urine and tissue samples from patients suspicious of bladder cancer and undergoing first TURB within BRIDGister RealWorld Experience trial. **Methods:** FFPE samples from the first TURB of 39 pts participating in the BRIDGister trial and matched urine samples were prospectively collected and analyzed. RNA from FFPE tissues were extracted by commercial kits and analyzed by Therascreen FGFR IVD kit (Qiagen GmbH, Hilden). In addition extracellular vesicles were centrally isolated for subsequent RNA extraction (exoRNA.Exosome Diagnostics GmbH, Martinsried) and centrall analysis by QIAcuity digital PCR (Qiagen, Hilden). In addition mRNA based profiling of urine was done by dPCR. Concordance, Spearman, Kruskal-Wallis and MannWhitney were analyzed by JMP 9.0.0 (SAS software). **Results:** The pilot cohort of the BRIDGister trial consisted of 39 patients (median age: 75, male 69% vs female 31%) of diverse clinical stages (Benign lesions/no tumor 23%, pTa 31%, pT1 26%, pT2 21%) and WHO 1973 grade (G1 8%, G2 39%, G3 34%). Based on FFPE tissue testing using Therascreen FGFR IVD kit and exosomal RNA extraction follwoed by dPCR 12 out of 39 patients exhibited FGFR alterations (31%). Comparison with tissue testing as probable gold standard revealed 67% sensitivity, 85% specificity, 67% PPV and 85%NPV. There were 4 patients being FGFR positive for exoRNA from urine with no mutation found in the corresponding TUR biopsy. Determining ERBB2 mRNA by dPCR from urine revealed that high ERBB2 mRNA correlated with higher WHO1973grade, while high FGFR3 mRNA correlated with lower grade tumors (Spearman r=0.4386 p=0.0075 and r=-0.4663 p=0.0042). Similiarly, trends were seen for association of ERBB2 and FGFR3 mRNA with clinical stage tumors in this pilote cohort (Spearman r=0.2359 p=0.0923 and r=-0.2249 p=0.1089). **Conclusions:** Extraction of exosomal RNA from urine followed by highly sensitive dPCR mutation testing is feasible with good concordance to matched tissue testing. Urine testing might evolve as alternative approach for FGFR3 screening in a non invasive fashion without the need of transurethral biopsy. Interestingly, mRNA assessment of exosomal RNA from urine before TURB correlated with clinical parameters such as WHO Grade 1973 with ERBB2 mRNA being associated with high grade tumors and FGFR3 mRNA being associated with low grade tumors, which is in line with previous tissue tsting results. This indicates the potential to clinically characterize tumor grade and stage before TUR biopsy or surgery which might be helpful for future risk stratification and planning of surgical intervention. Further exploration is warranted and includes the potential of monitoring patients with regard to urine based mutation detection and risk stratification. Research Sponsor: Qiagen.

Real-world treatment patterns, survival outcomes, and health care resource utilization among individuals with nonmuscle-invasive bladder cancer in Canada.

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Background: Real-world evidence pertaining to high-risk Non-Muscle Invasive Bladder Cancer (NMIBC) is limited. We aimed to describe real-world treatment patterns and outcomes of this study population within a Canadian setting. **Methods:** A retrospective cohort study was conducted by linking various population-based administrative datasets from a large Canadian province. The study population consisted of all individuals ≥ 18 years who were diagnosed with Tis or high-grade Ta/T1 NMIBC in Alberta, Canada between 2010-2019. High-grade disease was defined using the WHO 1973 system. Individuals who initiated BCG therapy were classified as having received adequate induction therapy if they completed 5+ cycles. BCG unresponsive was defined as receipt of TURBT, intravesical chemotherapy, cystectomy, or radiation within 1 year of the last BCG dose. Overall survival (OS), cystectomy-free survival (CFS), progression-free survival (PFS), and healthcare resource utilization (HCRU) were examined from the time of being classified as BCG unresponsive following adequate induction therapy. CFS was defined as time until death or radical cystectomy and PFS was defined as time until death or disease progression. Disease progression was classified using a proxy based on subsequent receipt of cystectomy, systemic therapy, or radiation. Kaplan-Meier survival curves were estimated for OS, CFS, and PFS and the mean number of healthcare encounters within each year of follow-up were estimated for HCRU. **Results:** 5369 individuals were diagnosed with NMIBC in Alberta between 2010-2019, of whom 2679 (49.9%) had Tis or HG Ta/T1 disease at initial diagnosis. Among individuals with high-risk NMIBC, 1044 (39%) initiated BCG therapy. 885 (84.8%) individuals received 5+ BCG doses. Despite receiving adequate induction treatment, 249 (28.1%) individuals became unresponsive. The mean age at BCG unresponsive was 72.9 years and 213 (58.5%) were males. Among those who were BCG unresponsive, 25.7% underwent radical cystectomy (median time to cystectomy: 4.4 months, IQR: 1.7 to 8.2). Median OS was 50.7 months (95% CI: 37.2-65.5), CFS was 22.4 months (18.9-31.1), and PFS was 14.4 months (11.6-20.9). Within the first year of becoming BCG unresponsive, individuals spent an average of 6.2 days in hospital, had 28.8 visits with healthcare practictitioners, and had 2.2 emergency and 13.6 non-emergency encounters with ambulatory care services. **Conclusions:** A considerable proportion of individuals with high-risk NMIBC became unresponsive to BCG therapy despite adequate treatment. The time from becomining BCG unresponsive to radical cystectomy was relatively short. These findings highlight an unmet need in this patient population for alternative therapeutic options. Research Sponsor: Ferring Inc.

471 **Poster Session**

Prospective validation of urine based FGFR screening by Uromonitor within the real-world clinicopathological register trial BRIDGister.

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Background: The objective of the present study was to prospectively evaluate FGFR mutation detetion in matched urine and tissue samples from patients suspicious of bladder cancer and undergoing first TURB within the framework of the BRIDGister RealWorld Experience trial. **Methods:** For this pilot study paraffin fixed pretreatment tissue samples from the first TURB of 48 pts participating in the BRIDGister trial and matched urine samples were prospectively collected and analyzed. RNA from FFPE tissues were extracted by commercial kits and analyzed by Therascreen FGFR IVD kit (Qiagen GmbH, Hilden). In addition urine samples were filtered at local urology and filters were shipped for central extraction of cellular DNA (Uromonitor, Porto). Concordance, Kruskal-Wallis, MannWhitney and Sensitivity/Specificity tests were analyzed by JMP 9.0.0 (SAS software). **Results:** The pilote cohort of the BRIDGister trial consisted of 47 patients (median age: 77, male 65% vs female 35%) of diverse clinical stages (benign lesions/no tumor 38%, pTa 23%, pT1 20%, pT2 19%) and WHO 1973 grade (G1 11%, G2 43%, G3 23%). Based on FFPE tissue testing using Therascreen FGFR IVD kit 10 out of 47 patients exhibited FGFR alterations (25%), while urine filtering for cellular components and subsequent PCR testing revealed 13 out of 40 matched urine sampels were FGFR positive (33%). Comparison with tissue testing as probable gold standard revealed 100% sensitivity, 90% specificity, 77% PPV, 100% NPV as well as high concordance (kappa 0,82, $p < 0,0001$). There were 3 patients being FGFR positive for Uromonitor from urine with no mutation found in the corresponding TUR biopsy. **Conclusions:** Filtering urine for cells and subsequent DNA extraction followed by PCR detection results in highly sensitive mutation testing being feasible with good concordance to matched tissue testing. Prospective testing validated the diagnostic accuracy of the Uromonitor FGFR test in a real world setting. Research Sponsor: None.

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Association of Medicaid expansion with racial disparities in timely neoadjuvant chemotherapy (NAC) in muscle-invasive bladder cancer (MIBC).

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Background: Timely initiation of NAC is critical to improve outcomes in MIBC. Medicaid expansion through the Affordable Care Act improved racial disparities in healthcare access for patients with advanced cancers. This study aimed to assess the association of Medicaid expansion with racial disparities in time-to-NAC in MIBC. **Methods:** This case-control study queried the National Cancer Database for 18-64 years old Black and White adults who were diagnosed with stage II&III bladder cancer and treated with NAC from Jan 1, 2008 to Dec 31, 2018. The primary endpoint was the timely receipt of NAC, defined as initiation within 45 days from the diagnosis of resectable MIBC. Racial disparity was defined as percentage-point (PP) difference for Black vs. White patients, adjusted for age, sex, income level, clinical stage, and year of diagnosis. **Results:** The study included 5053 patients (7.2% Black, n = 391). In states without Medicaid expansion, Black patients became less likely to receive timely NAC than their White counterparts (2008-2013: Black 59.6% vs White 63.8%, $p = 0.53$; 2014-2018: Black 47.9% vs White 61.2%, $p < 0.01$). In contrast, the racial disparity was narrowed in states with Medicaid expansion (2008-2013: Black 35.7% vs White 62.9%, $p < 0.01$; 2014-2018: Black 53.4% vs White 59.5%, adjusted PP difference -2.4; $p = 0.20$). The adjusted difference-in-differences estimate revealed a 26.0 PP reduction in racial disparity (95% CI, 8.1%-44.0%; $p < 0.01$). **Conclusions:** Medicaid expansion was associated with significant reduction in racial disparity between Black and White patients in the timely receipt of NAC for MIBC. Research Sponsor: None.

Contemporary analysis of cystectomy complications.

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Background: Radical cystectomy (RC) is a curative treatment for patients with invasive bladder cancer, but carries significant morbidity. Modern improvements in perioperative care have decreased length of stay (LOS) without effect on complication or readmission rates. Herein, we examine contemporary changes in complication rates of RC. **Methods:** The National Surgical Quality Improvement Program (NSQIP) database was queried for RC performed from 2006-2018 for nondisseminated bladder cancer identified by CPT, ICD-9 and 10 codes. Demographics and outcomes were studied across time periods: 2006-2011, 2012-2014 and 2015-2018. 30 day complications were classified as minor (urinary tract infection (UTI), superficial incisional surgical site infection (SSI), pneumonia, blood transfusion) or major (readmission, reoperation, sepsis/septic shock, deep vein thrombosis (DVT), stroke, reintubation, renal failure, myocardial infarction, pulmonary embolus (PE), dehiscence, cardiac arrest, deep incisional SSI, organ/space SSI, death). **Results:** We identified 11,351 RC performed during the study period. Baseline characteristics were similar across the different time periods. Mean length of stay (10.5, 9.8 and 8.6 days, respectively, $p<0.001$) decreased over time while readmission (20.0, 21.3, and 21.0%, respectively) and mortality rates were stable (2.7, 1.7, 2.0%, respectively). There was a significant decrease in overall minor complications over time, including superficial SSIs and transfusions (Table). The rate of major complications decreased over time, though not statistically significantly. Deep SSIs and PEs significantly decreased, while sepsis rates remained stable and high over time (Table). Rates of UTI was stable over time (10.1%, 8.8%, 8.3%, respectively, p=0.11). **Conclusions:** An analysis of the contemporary era shows continued decrease in LOS after RC and a decrease in overall complications. This may reflect beneficial effects of changes in perioperative bladder cancer management such as increased use of neoadjuvant chemotherapy, enhanced recovery after surgery protocols and laparoscopic/robotic techniques. Further efforts to improve care must target infectious complications and readmissions. Research Sponsor: U.S. National Institutes of Health.

Postoperative complications.

	2006-2011 (n=1055)	2012-2014 (n=3170)	2015-2018 (n=7126)	P
Any Complication	596 (56.5%)	1820 (57.4%)	3607 (50.6%)	<0.001
Major Complication	275 (26.1%)	784 (24.7%)	1684 (23.6%)	0.154
Minor Complication	489 (46.4%)	1554 (49.0%)	2920 (41.0%)	<0.001
30-day Mortality	28 (2.7%)	53 (1.7%)	139 (2.0%)	0.133
Superficial Incisional SSI	69 (6.5%)	196 (6.2%)	328 (4.6%)	<0.001
Deep Incisional SSI	20 (1.9%)	67 (2.1%)	55 (0.8%)	<0.001
PE	32 (3.0%)	71 (2.2%)	104 (1.5%)	<0.001
Intraop/Postop Transfusion	361 (34.2%)	1268 (40.0%)	2258 (31.7%)	<0.001
Sepsis	110 (10.4%)	280 (8.8%)	623 (8.7%)	0.197

Long-term outcome and safety in patients treated with immune checkpoint blockade therapies for urothelial carcinoma: Experience from real-world clinical practice.

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Background: Anti-tumor activity and manageable safety profile of immune checkpoint blockade therapies (ICT) have been demonstrated in previous clinical trials in patients with metastatic urothelial carcinoma. To the best of our knowledge, very limited real-life data is available with the long follow-up time that confirms the durable antitumor activity and safety of ICT. In this study, we reported the real-life results of 56 months follow-up data of urothelial carcinoma patients who were treated with ICT. **Methods:** Metastatic urothelial carcinoma patients treated with at least one course of ICT included in the study. The primary endpoint was the overall response rate (ORR); secondary endpoints were overall survival (OS), progression-free survival (PFS), duration of the ICT treatment, and safety. Median follow-up, PFS, and OS were estimated by using the Kaplan-Meier method. **Results:** Data of 185 eligible patients were analyzed, 11.9% of these patients received the ICT as the first line, 76.8 % as the second line, and 11.3 % as the third or more line of treatment. The median age of the patients was 66 years, and 156 (84.3%) were male (37-86). The majority of patients (93.5%) had ECOG PS scores of 0–1 and primary tumor in the bladder was predominant (86.7%). The median follow-up time was 47(1.15-56) months. The complete response rate to ICT, partial response rate, and ORR were 10.3% (n = 19), 19.5% (n = 36), and 29.8% (n = 55), respectively. The median duration of response was 33.1 months (95% CI, 16.5–49.7). Of the fifty-five patients who responded to treatment, 28 (51%) had an ongoing response at the time of the analysis. Median PFS and OS was 3.8 (2.6–5.1) months and 8.9 (6.8–11.1) months, respectively. 56-month PFS and OS rate was 9.2% and 11.4%, respectively. 56-month PFS and OS rate for CR and PR was 56.2% and 20%, respectively. Fifty-nine percent of patients experienced a treatment-related adverse event of any grade, and 32 (17.3%) of patients had a grade 3–4 treatment-related adverse event. Because of treatment-related side effects, treatment was discontinued in 8 (4.3%) patients and adverse event that required systemic steroid use was reported in only 13 (7%) patients. Four patients (2.2%) died due to treatment-related causes. **Conclusions:** This 56-month analysis of real-world data confirms the durable response and long-term survival with ICT in metastatic urothelial carcinoma patients. The safety profile was consistent with prior reports, and no new safety signals emerged. Research Sponsor: None.

475 **Poster Session**

The prognostic impact of preoperative health-related quality life on bladder cancer-specific survival in patients treated with radical cystectomy.

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Background: Previous studies have shown that baseline health-related quality of life (HRQOL) is a valuable prognostic indicator of survival outcomes for various cancer entities in the metastatic setting, yet there is no evidence on the prognostic value of baseline HRQOL for patients undergoing radical cystectomy (RC) with curative intent. The goal of this study was to evaluate the influence of baseline preoperative HRQOL on cancer specific survival prognosis for patients undergoing RC. **Methods:** 407 patients with prospectively assessed baseline HRQOL prior RC were included. Patients were stratified by the global health status (GHS) domain of the EORTC QLQ-C30 questionnaire, and good general HRQOL was defined as GHS≥70 based on validated cut-off levels. A 1:2 propensity-score-matched analysis of n=357 patients [n=125 (GHS≥70), n=232 (GHS<70)] was performed. Primary endpoint was cancer-specific survival (CSS), secondary endpoints encompassed overall survival (OS) and recurrence-free survival (RFS). Multivariate Cox regression models were performed to assess prognostic significance of baseline GHS on survival outcomes. Harrell's discrimination C-index was assessed to calculate the predictive accuracy of the model ($p<0.05$). **Results:** Median follow-up was 40.5mo. Patients subcohorts were well-balanced. All baseline QLQ-C30 functioning scales were in favour of the GHS≥70 cohort (each $p<0.001$). 5-yr CSS (82% vs. 65%; p=0.001), 5-yr OS (76% vs 53%; p=0.001) and 5-yr-RFS (50% vs. 39%; p=0.04) and were significantly increased in the GHS≥70 cohort. GHS≥70 was confirmed as an independent predictor for increased CSS (HR 0.43, 95%CI 0.21–0.89; p=0.028), OS (HR 0.56, 95%CI 0.31–0.90; p=0.031) and RFS (HR 0.52, 95%CI 0.31–0.87; p=0.013) multivariate analysis. **Conclusions:** Our findings suggest preoperative baseline HRQOL to have a pronounced predictive value for patients undergoing RC with curative intent for bladder cancer. We found baseline good general HRQOL to accurately predict increased CSS, OS and RFS. Research Sponsor: None.

Univariate & Multivariate Cox Regression Analysis of bladder cancer specific survival.

			95% CI						95% CI		
	Parameter	HR	Lower	Upper	p value		Parameter	HR	Lower	Upper	p value
univariate	GHS ≥ 70	0.406	0.22	0.74	0.003	multivariate	GHS ≥ 70	0.433	0.21	0.89	0.028
	PF scale	0.978	0.96	0.99	<0.001		PF scale	0.988	0.97	1.08	0.086
	pT-stage	2.516	1.85	3.42	<0.001		pT-stage	1.773	1.30	2.43	<0.001
	positiv surgical margin	4.534	2.81	7.32	<0.001		positiv surgical margin	2.179	1.04	4.55	0.038
	Lymph node involvement	2.611	1.55	4.41	<0.001		Lymph node involvement	1.388	0.76	2.73	0.283
	ASA	2.250	1.21	4.18	0.010		ASA	4.485	2.02	9.95	<0.001
	Age (yr)	1.033	1.01	1.06	0.023		Age (yr)	1.001	0.97	1.03	0.966
	BMI	1.004	0.94	1.07	0.894						

Changes in body composition during neoadjuvant platinum-based chemotherapy associations prior to radical cystectomy: Implications for chemotherapy-associated adverse events and oncologic outcomes.

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Background: Low skeletal muscle index (SMI) is associated with an increased risk of mortality in muscle-invasive bladder cancer (MIBC) and chemotherapy-related adverse events (AE) across numerous other malignancies. Small case series suggest neoadjuvant chemotherapy (NAC) is associated with a significant decline in SMI in patients with MIBC. However, limited data exists regarding changes in fat mass during NAC. Herein, we examine changes in SMI, visceral fat index (VFI), and subcutaneous fat index (SFI) in patients receiving NAC for MIBC before radical cystectomy (RC). We describe associations between body composition changes and NAC-associated AE and all-cause mortality (ACM) in patients with MIBC. **Methods:** Retrospective review of patients with MIBC (≥pT2 N0/x/1 M0) who received NAC (2006-2019). Patients with digitized abdominal computed tomography scans (CT) within 75 days prior (T1) and 75 days following completion (T2) of NAC were included. We segmented and calculated the indices (cm^2/m^2) for SMI, VFI, and SFI at the third lumbar vertebra level at T1 and T2 using validated methodology. Associations with AE during NAC and ACM were evaluated with multivariate logistic regression and Cox proportional hazards models. **Results:** Included 170 patients, median age 63 years receiving a median of 4 (IQR 3-5) cycles of Gemcitabine/Cisplatin (52%), MVAC (28%), or other NAC (20%). Absolute and relative changes in SMI, VFI, and SFI over a median of 112 days (IQR 94-146) between measurements are presented in the Table. 117 (69%) patients experienced grade ≥3 chemotherapy-related AE. No associations between baseline body composition or change in body composition during NAC with chemotherapy-related AE. T1 SMI (HR: 0.98; 0.97-0.99, p = 0.008), as well as T2 SMI (HR: 0.98; 0.96-0.99, p = 0.003), T2 VFI (HR: 0.99; 0.99-1.0, p = 0.05) and T2 SFI (HR: 0.99; 0.98-1.0, P = 0.03) were associated with ACM after adjusting for age, clinical T and N stage, and performance status. **Conclusions:** Patients undergoing NAC prior to RC experienced a 6.4% decrease in SMI and a 5.2% decrease in VFI during an average of 112 days. Chemotherapy-related AE were not associated with a change in body composition. Baseline SMI and T2 SMI, SFI, and VFI were associated with ACM on multivariable analysis. Future work is needed to understand the mechanisms underpinning such changes and the extent to which potentially detrimental changes in body composition may be mitigated before surgery. Research Sponsor: None.

Body Composition Variable	Pre-NAC (median, IQR)	Post-NAC (median, IQR)	Change	Relative Change	P-value (Paired Wilcoxon Rank Sum)
SMI (cm^2/m^2)	49.3 (41.6, 55.3)	46.1 (41.1, 53.1)	-3.17	-6.4%	< 0.01
Muscle density (HU)	41 (34, 47)	42 (34, 47)	+1	+2.4%	0.81
VFI (cm^2/m^2)	54.8 (31, 86.6)	51.9 (27, 82.8)	-2.89	-5.2%	0.04
SFI (cm^2/m^2)	54 (33.7, 75.1)	54.4 (33.6, 75.3)	+0.47	+0.9%	0.45

477 **Poster Session**

Survival outcomes comparing radical nephroureterectomy versus endoscopic treatment in solitary kidney patients diagnosed with upper tract urothelial carcinoma.

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Background: Solitary kidney patients who develop upper tract urothelial carcinoma (UTUC) present a significant management challenge. Radical nephroureterectomy (RNU) renders these patients anephric with a need for dialysis, which is associated with lower life expectancy and decreased quality of life. However, organ-sparing endoscopic treatment may result in undertreatment of the cancer process. We sought to compare survival outcomes between RNU and endoscopy in solitary kidney patients diagnosed with clinically localized UTUC. **Methods:** The Surveillance, Epidemiology, and End Results database was linked to Medicare records to identify patients diagnosed with UTUC through 2017. This data was then linked to the Medicare Provider Analysis and Review and National Claims History databases to identify patients with a solitary kidney. Only patients with an established diagnosis of solitary kidney prior to developing clinically node-negative and non-metastatic disease (cN0M0) UTUC were included. Patients were stratified by treatment with RNU versus endoscopy. Kaplan-Meier analysis was performed to estimate survival between the two groups. **Results:** A total of 2108 solitary kidney patients with cN0M0 UTUC were identified, with a median age of 75.3 years at diagnosis [IQR 69.3-81.1]. Median follow-up time was 2.8 years [IQR 1.7-4.4]. High-grade disease was present in 1531 patients (72.6%), of whom 1344 underwent RNU and 195 underwent endoscopy. Between the two treatments, there was no difference in either cancer-specific survival (P=0.18) or overall survival (P=0.10). When combining high- and low-grade UTUC patients, 1839 underwent RNU and 269 underwent endoscopy. Again, no difference was observed in cancer-specific survival (P=0.31) or overall survival (P=0.17). Patients with high-grade disease demonstrated higher rates of cancer-specific and overall mortality than those with low-grade disease (both $P<0.001$). **Conclusions:** Solitary kidney patients diagnosed with clinically localized UTUC demonstrate no difference in survival outcomes when comparing RNU to endoscopic treatment. This potentially suggests that, when weighed against the option of endoscopic treatment, the benefits of RNU in these patients may not outweigh the risks of becoming anephric and therefore dependent on dialysis. Research Sponsor: None.

Risk of secondary malignancies after pelvic radiation: A population-based analysis.

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Background: Radiation therapy (RT) is an integral component of the multimodal therapy of pelvic malignancies, either as primary treatment or in combination with surgical resection. In addition to local treatment effects on nearby pelvic organs, RT has been established to be a risk factor for delayed secondary malignancies. In this study, we examine the rate of any secondary malignancies following RT for primary pelvic malignancies, with a specific emphasis on secondary pelvic malignancies **Methods:** Using the SEER (Surveillance, Epidemiology, and Ends Results) database, we retrospectively examined 2,102,192 patients with primary pelvic malignancies (prostate, bladder, uterine, rectal, cervical). For each disease site, we compared the rate of all secondary malignancies in radiated patients to non-radiated patients. Secondary malignancies were then stratified as pelvic and non-pelvic, in order to determine the local effect of RT on malignancy risk. **Results:** A total of 2,102,192 patients were examined (1,189,108 prostate, 315,026 bladder, 88,809 cervical, 249,535 uterine, 259,714 rectal). A total of 113,322 patients developed secondary malignancies after RT (Table), with 26,299 developing secondary pelvic malignancies after RT (18,411 prostate, 1,026 bladder, 1,410 cervical, 2,179 uterine, 3,273 rectal) (Table). The overall relative risk (RR) of RT on developing a secondary malignancy was 1.79 (1.77-1.80 CI, P<0.0001), particularly in patients with prostate (RR 2.57), uterine (RR 1.24) and cervical cancer (1.09). The overall RR of RT on developing a secondary pelvic malignancy was 2.09 (2.06-2.13 CI, P<0.0001), particularly in patients with bladder (RR 6.90), prostate (RR 2.74), and uterine cancer (RR 1.21). **Conclusions:** Radiation treatment for pelvic malignancies increases the risk of developing secondary malignancies over the patient's lifetime. Further work needs to done to identify at risk populations. Research Sponsor: None.

PRIMARY MALIGNANCY TYPE	TOTAL NUMBER OF PATIENTS	Rate of Secondary Malignancy amongst RT patients Rate (%)	Rate of Secondary Malignancy amongst non-RT patients Rate (%)	RR	Rate of Secondary Pelvic Malignancy amongst RT patients Rate (%)	Rate of Secondary Pelvic Malignancy amongst non-RT patients Rate (%)	RR
ALL	2102192	113322/619186 (18.3)	151826/1483006 (10.2)	1.79	26299/619186 (4.2)	30076/1483006 (2.0)	2.09
BLADDER	315026	2444/18068 (13.5)	42317/296958 (14.3)	0.95	1026/18068 (5.7)	2444/296958 (0.8)	6.9
CERVICAL	88809	3935/45747 (8.6)	3405/43062 (7.9)	1.09	1410/45747 (3.1)	1551/43062 (3.6)	0.86
PROSTATE	1189108	90155/386147 (23.3)	73028/802961 (9.1)	2.57	18411/386147 (4.8)	13970/802961 (1.7)	2.74
RECTAL/ANAL	259714	9739/98383 (9.9)	18743/161331 (11.6)	0.85	3273/98383 (3.3)	7573/161331 (4.7)	0.71
UTERINE	249535	7049/70841 (9.9)	14333/178694 (8.0)	1.24	2179/70841 (3.1)	4538/178694 (2.5)	1.21

Rate of secondary malignancies after radiation.

479 **Poster Session**

Prospective evaluation of a comprehensive geriatric assessment (CGA) in multidisciplinary bladder cancer care: Feasibility and impact on decisional conflict.

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Background: Commonly utilized risk stratification tools demonstrate inconsistent associations with salient clinical outcomes in bladder cancer leading to a disproportionate reliance on providers' subjective impression of a patient's fitness for therapy. Current guidelines advocate for use of a CGA to quantify vulnerabilities in older ($>$ 65 years) patients before treatment selection. Our objective was to prospectively evaluate CGA in our Bladder Cancer Multidisciplinary Clinic (BCMC). We hypothesized that CGA implementation would be feasible and that discussion of the results during shared decision-making would be associated with reduced patient-reported decisional conflict. **Methods:** Patients seen in BCMC were prospectively enrolled from 6/1/20 to 7/20/21. In the first 3 months, participants underwent non-standardized risk stratification ("Routine cohort", N = 27). Between 9/1/20 and 7/20/21, participants completed a CGA incorporating validated assessments of frailty, functional status, multimorbidity, nutrition, cognition, and mental health ("CGA cohort", N = 67). Results were shared with patients during BCMC visits. All patients and providers (three physicians per clinic from: Uro-Oncology, Medical Oncology, and Radiation Oncology) completed a follow-up survey including the Decisional Conflict Scale (DCS). Time required to complete the CGA, completion rates, and patient-reported burden were assessed. Concordance of patient- and provider-reported decisional conflict was compared between Routine and CGA cohorts. **Results:** Of 138 eligible patients, 94 patients were successfully enrolled (68%) with median age of 72 years, ECOG PS $\geq$3 in 13%, and Charlson Comorbidity Index $\geq$3 in 18%, of whom 18% were women. Most patients had pT2 bladder cancer (87%; cN+ and M1 in 23.4% and 9.6%, respectively). CGA component completion rates were 79-100%. Survey response rates were high (patients: 77%, providers: 86%), and most (86%) patients felt that the CGA was, at most, minimally burdensome. Vulnerabilities detected across CGA domains triggered relevant referrals. Patient-reported median (IQR) DCS scores were numerically higher (e.g. greater decisional conflict) for the CGA cohort: (27 [14-33] vs 16 [2-30] for Routine patients, p = 0.28). Provider- and provider reported DCS score was correlated in the CGA (p = 0.04), but not the Routine cohort (p = 0.07). **Conclusions:** We prospectively evaluated use of CGAs in bladder cancer care and found that CGAs were successfully implemented with high rates of completion and low rates of perceived burden. Notably, in this pilot cohort of 94 patients, DCS scores did not differ significantly between patients and providers with CGA use. Future work will evaluate associations between individual instruments, treatment decisions, clinical outcomes and patient-reported quality of life measures. Research Sponsor: Bladder Cancer Advocacy Network Young Investigator Award.

Distribution of immune-related adverse events (irAEs) across genitourinary (GU) malignancies.

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Background: Checkpoint inhibitors (CPIs) targeting PD-1/PD-L1 and CTLA-4 have revolutionized management of GU malignancies. These agents are associated with a unique subset of toxicities that are immune-mediated, with a broad clinical spectrum that may affect any organ. Patients can also experience $^{3}1$ irAE involving multiple organ systems. Individual patient susceptibilities and type of CPI used may influence the incidence and type of irAEs that may develop. Wehypothesize that there are also differences in irAEs based on the histologic malignancy subtype. **Methods:** We performed a retrospective analysis of all patients with GU malignancies who received CPIs at the University of California Irvine using an outpatient oncology pharmacy database. Data was collected from 1/1/2020 to 6/30/2021. Patients were aged $^{3}18$ years and had a diagnosis of urothelial carcinoma (UC), renal cell carcinoma (RCC), prostate adenocarcinoma, or penile squamous cell carcinoma. Patients must have received $^{3}1$ dose of a CPI agent including ipilimumab (I), nivolumab (N), pembrolizumab (P), atezolizumab (At), avelumab (Av), durvalumab (D), and cemiplimab (C). **Results:** A total of 128 patients who received 141 unique CPI regimens were included. Documented irAEs were noted in 50.0% of patients and 18.4% had $^{3}1$ irAE. A total of 99 unique irAEs were recorded. In those who experienced irAEs, 92.2% of patients received CPIs in the metastatic setting and 7.8% in the adjuvant setting. In those who experienced irAEs, 12.5% of patients received combination CPIs with I+N, while 87.5% received single-agent CPI. In those who experienced irAEs, 46.8% of patients had UC, 50.0% had RCC, 1.6% had prostate cancer, and 1.6% had penile cancer. In those who experienced irAEs, 24.2% had skin rash or pruritis, 23.2% had endocrinopathies, 14.1% had colitis, 13.1% had other toxicity including arthritis, 12.0% had hepatitis, 3.9% had myositis, 2.9% had pneumonitis, 1.9% had neurologic toxicity including myasthenia gravis and encephalitis, 1.9% had carpal tunnel syndrome, 1.9% had nephritis, and 0.9% had autoimmune thrombocytopenia. Various irAEs for UC and RCC are summarized in Table. **Conclusions:** In this dataset, there were differences in type and incidence of irAEs in patients with UC and RCC, while the sample size was too small to draw conclusions about patients with prostate and penile cancer. Further investigation is needed involving other solid tumor types, including non-GU malignancies, to definitively answer this question. Research Sponsor: None.

Type and incidence of irAEs in patients with UC and RCC.

irAE type	UC (%)	RCC (%)
Skin rash/pruritis	34.8	14.3
Endocrinopathies	17.4	24.5
Colitis	10.9	14.3
Hepatitis	10.9	14.3
Other (including arthritis)	10.7	18.3
Myositis	4.3	4.1
Pneumonitis	2.2	2.0
Neurologic	2.2	4.1
Carpal tunnel syndrome	2.2	2.0
Nephritis	2.2	2.0
Thrombocytopenia	2.2	0

481 **Poster Session**

Association of changes in albumin levels with survival and toxicities in patients (pts) with metastatic urothelial carcinoma (mUC) receiving enfortumab vedotin (EV).

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Background: EV is an anti-Nectin-4 antibody-drug conjugate that has been approved by the US FDA for mUC progressing on platinum and PD1/L1 inhibitor therapy and in cisplatin-ineligible pts following prior therapy. However, prognostic and predictive biomarkers in the setting of EV therapy are unclear. We aimed to investigate baseline and early changes in commonly available clinical and laboratory tests that could help predict survival and toxicities in patients with mUC treated with EV. **Methods:** Data from patients with mUC who were treated with EV at Dana Farber Cancer Institute between 2017 and 2021 were reviewed retrospectively. We assessed the association of demographic (age, sex), clinical (ECOG-performance status [PS], sites of metastasis) and laboratory variables (hemoglobin, RDW, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, platelet count and serum albumin) at baseline as well as after 4-7 weeks of treatment with Overall Survival (OS) by constructing univariate and multivariable Cox proportional-hazards models. Any variables significantly associated with OS at the univariate level (using an alpha-level of 0.1 to determine statistical significance) were then entered into the multivariable model. Predictors were eliminated from the final multivariable models by a backward selection process, retaining only those with a p-value of ≤ 0.05. **Results:** A total of 49 patients who received EV were included in the analysis. The median age was 72 years (range 48-88) and 36 (73.5%) were male. The median OS was 13.3 months (range: 2.7-38.7) and grade 3-4 toxicities were seen in 11 pts (22.4%). In the final multivariable models, lower serum albumin at 4-7 weeks (HR = 0.18; 95% CI = 0.05-0.71; p = 0.015), and baseline ECOG-PS of 1 vs. 0 (HR = 2.56; 95% CI = 1.05-6.21; p = 0.038) were significantly associated with worse OS (Table). Patients with higher serum albumin levels at 4-7 weeks also had significantly lower odds of experiencing grade 3-4 adverse events on EV (OR = 0.05; 95% CI = 0.002-0.52; p = 0.02). **Conclusions:** Lower serum albumin appeared to predict worse survival and severe toxicities in mUC pts receiving EV. This information may guide therapy and assist in the prevention of toxicities. Additionally, ECOG-PS was prognostic while the location of metastatic disease was not prognostic in the setting of EV. Research Sponsor: None.

	HR	95% CI	P-value
ECOG PS of 1	2.56	1.05 - 6.21	0.038
Albumin at 4-7 weeks	0.18	0.05 - 0.71	0.015

BCG efficacy in nonmuscle-invasive bladder cancer after prior radiation treatment for prostate cancer.

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Background: Prostate radiotherapy is associated with worse oncologic outcomes in patients with bladder cancer. This is thought to be secondary to microvascular damage resulting in propagation of inflammation. There is sparse data on the effect of prior radiotherapy on the efficacy of intravesical *Bacillus Calmette-Guerin (BCG)* in patients with non-muscle invasive bladder cancer (NMIBC). We sought to evaluate BCG response and outcomes in NMIBC patients who have previously undergone prostate radiotherapy compared to patients with no prior history of pelvic radiotherapy. **Methods:** This is a retrospective cohort study that includes patients who received intravesical BCG for NMIBC at our institution from 2001 to 2019. Data were collected on patient and pathologic characteristics. Patients were stratified into three cohorts: prior radiotherapy (RT), radical prostatectomy (RP), and no prostate cancer (No PCa). Wilcoxon rank sum test and Chi-squared test were used for comparison between groups. The primary endpoints included recurrence at one-year, progression to MIBC and progression to metastatic disease. **Results:** In 199 total patients who underwent BCG for NMIBC, 23 had a prior history of radiotherapy treatment for prostate cancer, while 17 underwent prior radical prostatectomy. Overall, 41.2% of patients had recurrence at one year. There was no difference in recurrence at one year between the cohorts: 42.8% No PCa, 29.4% RP and 39.1% RT; p = 0.56. There was also no difference in progression to MIBC (6.9% No PCA, 0% RP, and 8.7% RT) or progression to metastatic disease (6.9% No PCA, 5.9% RP and 4.3% RT) with p = 0.50 and 0.89 respectively. **Conclusions:** The efficacy of intravesical BCG does not appear to be modified by prior radiation treatment for prostate cancer in patients with NMIBC. Research Sponsor: None.

	No PCa Hx (N=159)	PCa Resected (N=17)	PCa RT (N=23)	Total (N=199)	p value
Age					0.08
n	159	17	23	199	
Median	72	78	77	73	
Q1, Q3	68.00, 79.00	65.00, 81.00	72.00, 82.00	68.00, 80.00	
Mean (SD)	72.45 (9.85)	75.47 (9.55)	77.13 (7.79)	73.25 (9.71)	
Current/former smoker	116 (73.0%)	8 (47.1%)	17 (73.9%)	141 (70.9%)	0.08
Initial tumor size (cm)					0.25
n	154	17	22	193	
Median	1.2	0.7	0.9	1	
Q1, Q3	0.42, 2.38	0.40, 1.50	0.60, 1.45	0.50, 2.00	
Mean (SD)	1.61 (1.44)	1.04 (0.90)	1.16 (0.89)	1.51 (1.36)	
Initial pathology					0.76
Cis	27 (17.0%)	2 (11.8%)	2 (8.7%)	31 (15.6%)	
T1	48 (30.2%)	4 (23.5%)	7 (30.4%)	59 (29.6%)	
Ta	84 (52.8%)	11 (64.7%)	14 (60.9%)	109 (54.8%)	
Variant histology					0.55
No	144 (90.6%)	14 (82.4%)	21 (91.3%)	179 (89.9%)	
Yes	15 (9.4%)	3 (17.6%)	2 (8.7%)	20 (10.1%)	
Recurrence at 1 year					0.56
No	91 (57.2%)	12 (70.6%)	14 (60.9%)	117 (58.8%)	
Yes	68 (42.8%)	5 (29.4%)	9 (39.1%)	82 (41.2%)	
High Risk Recurrence	35 (22.0%)	4 (23.5%)	6 (26.1%)	45 (22.6%)	
Progression to MIBC					0.50
No	148 (93.1%)	17 (100.0%)	21 (91.3%)	186 (93.5%)	
Yes	11 (6.9%)	0 (0.0%)	2 (8.7%)	13 (6.5%)	
Progression to metastatic disease					0.89
No	148 (93.1%)	16 (94.1%)	22 (95.7%)	186 (93.5%)	
Yes	11 (6.9%)	1 (5.9%)	1 (4.3%)	13 (6.5%)	

SUB-urothelial durvalumab injection: 1 (SUBDUE-1)—Results from the first nine urothelial cancer patients using a dose-escalation schedule.

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Background: The sub-urothelial administration of checkpoint inhibitors has not been reported. This approach could be safer and more efficacious than systemic delivery for patients with non-muscle-invasive bladder cancer (NMIBC). **Methods:** This phase 1b study employed a 3+3 dose-escalation design to explore tolerability, safety and immunological efficacy of sub-urothelial durvalumab, a programmed death-ligand 1 (PDL1) monoclonal antibody. Eligible participants had high risk NMIBC or MIBC without prior chemotherapy or immunotherapy (BCG allowed) and were planned for cystectomy. Participants received 25/75/150mg durvalumab diluted in 25mL normal saline injected into the sub-urothelium at 25 locations (25x1mL injections), at least 2 weeks prior to radical cystectomy. Systematic four quadrant cold cup bladder biopsies were taken immediately prior to durvalumab injection and immediately prior to cystectomy. Tumour, if present, was biopsied before and after injection and bladder maps recorded. International Prostate Symptom Index (IPSS) and O'Leary symptom score at various time points and adverse events (AE) as per CTCAE (Version 4) were recorded. Relative changes in immune cell counts (RCI) on bladder biopsy for CD3, CD8, CD68 and CD168 expressing cells are reported (value >1.0 designating increase). **Results:** Nine participants were recruited; eight male (89%), 1 female; mean age 72 years (range 56 – 82). No dose-limiting toxicities were observed. No evidence of treatment-related effect on IPSS or O'Leary Symptom scores was seen. Fourteen AEs were reported by six (67%) patients: 10 were Grade 1, 3 Grade 2, 1 Grade 3. None were considered immune- or treatment-related by investigators. Transient elevation of peri-operative thyroid stimulating hormone was seen in two subjects, which normalised without intervention. No hepatitis was seen. All patients underwent planned cystectomy. RCI of different immune populations was calculated (see Table). Visible tumour was present in only 4 patients limiting interpretation of RCI. RCI varied significantly between cell types (p=0.008*). RCI numerically increased by dose but did not reach statistical significance (p=0.076**). A numeric increase in monocytes was seen at 150mg dose. RCI of different immune populations by dose of sub-urothelial durvalumab. **Conclusions:** Sub-urothelial injection of durvalumab was safe at all 3 dose levels without any drug-related adverse events. Immunological studies showed differential effects on immune cells with macrophage population most affected. Further studies investigating the role of 150mg sub-urothelial durvalumab in the management of NMIBC are planned. Clinical trial information: ACTRN12620000063910. Research Sponsor: Australia and New Zealand Urogenital and Prostate Cancer Trials Group., Other Foundation., Pharmaceutical/Biotech Company.

	Relative changes in immune cell count				
Dose	**CD3**	**CD8**	**CD68**	**CD168**	***Dose effect****
25mg	1.14	1.10	1.16	0.95	1.05
75mg	0.86	0.86	1.44	1.48	1.23
150mg	1.48	1.15	1.92	1.56	1.50
Cell effect**	1.15	1.04	1.50	1.33	

Atezolizumab for locally advanced/metastatic urothelial carcinoma within the compassionate use program in Spain: The IMcompass study.

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Background: Atezolizumab is a monoclonal antibody with proven efficacy in clinical trials for advanced or metastatic urothelial carcinoma (UC) after progression to platinum-based chemotherapy. Following EMA marketing authorization and before prizing and reimbursement was granted in Spain, the Spanish Medicines Agency authorized a compassionate use program. We describe the patient characteristics and atezolizumab effectiveness in this compassionate use program. **Methods:** It was a multicentre cohort study based on the retrospective chart review of patients with inoperable locally advanced or metastatic UC who received atezolizumab, following progression to platinum-based chemotherapy, under the compassionate use program in Spain. The primary endpoint was their demographic and clinical characterization. Secondary endpoints included the best response to atezolizumab, progression-free survival (PFS) and overall survival (OS). **Results:** 109 evaluable patients were included, with a median age (interquartile range, IQR) of 68.0 years (62.0-75.0), 87 males (79.8%) and 96 Caucasians (88.1%). Median age (IQR) at diagnosis was 64.0 years (58.0-72.0) and 92 (84.4%) had pure urothelial carcinoma. Twenty-four (22.0%) had received BCG, 18 (16.5%) neoadjuvant treatment, 19 (17.4%) adjuvant treatment, and 19 (17.4%) radiotherapy for primary tumour. Regarding prior metastatic treatments, 98 (89.9%) had received first-line chemotherapy, 46 (42.2%) second line, 19 (17.4%) third line, and 5 (4.6%) more lines. When starting atezolizumab, median age (IQR) was 69.0 years (62.0-74.0) and 105 (96.3%) had metastases: 71 (65.1%) in lymph nodes and 64 (58.7%) visceral (skeletal n = 31, lung n = 29, liver n = 26, other n = 13). Atezolizumab was used for a median (IQR) of 2.8 (1.4-8.4) months and 5.0 (3.0-13.0) administered doses. The overall response rate was 23.8%, with 6 patients (5.5%) achieving complete response and 20 (18.3%) partial response. Stable disease was observed in 21 (19.3%), progression in 44 (40.4%) and response was not evaluable in 18 (16.5%). The median PFS (95% CI) was 3.7 months (2.8-5.8), with PFS rates at months 3, 6, 9 and 12 of 57.5%, 38.0%, 30.5% and 26.1%, respectively. The median OS (95% CI) reached 8.5 (6.6-12.6) months, with a 12-month OS of 43.4%. Twenty-three patients (21.1%) reported 26 delays (adverse event n = 16, intercurrent event n = 10) and 2 (1.8%) interruptions (adverse event n = 1, intercurrent event n = 1). Atezolizumab was discontinued in 64 (58.7%) due to disease progression (n = 43, 67.2%), death (n = 13, 20.3%), adverse events (n = 7, 10.9%) and lost to follow-up (n = 1, 1.6%). **Conclusions:** This study provides real-world evidence on the characteristics of patients with advanced or metastatic UC treated with atezolizumab under the Spanish compassionate use program, supporting its effectiveness in the clinical setting. Research Sponsor: Roche Farma S.A.

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Impact of angiotensin-converting enzyme inhibitors (ACEi) on pathologic complete response with neoadjuvant chemotherapy (NAC) for muscle-invasive bladder cancer (MIBC).

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Background: The renin-angiotensin system (RAS) has been demonstrated to modulate cell proliferation, desmoplasia, angiogenesis and immunosuppression. Angiotensin pathway inhibitors are postulated to favorably reprogram the stroma in part by inhibition of transforming growth factor-β, a major mechanism of resistance, and have been previously reported to be associated with improved outcomes in the setting of immune checkpoint inhibitors (ICIs) for metastatic urothelial carcinoma (Jain R, Clin Genitourin Cancer 2021). In this analysis, we examined the association of angiotensin inhibitors in the setting of NAC for MIBC preceding radical cystectomy (RC). **Methods:** Pts with MIBC who received NAC preceding radical cystectomy were assembled from 3 institutions: Dana-Farber Cancer Institute (DFCI), Moffitt Cancer Center (MCC) and McGill University Health Center (MUHC). Pts were retrospectively assessed for the association of concurrent ACEi/angiotensin receptor blockers (ARB) use at initiation of NAC on pathologic complete response (pCR), defined as pT0N0, and overall survival (OS). Pathologic features, performance status (PS), clinical stage, type/number of cycles of NAC, and toxicities were collected. The Kaplan-Meier method was used to estimate OS. Logistic and Cox regression were used to explore factors potentially prognostic for pCR and OS respectively. **Results:** 302 MIBC pts who received NAC preceding RC were available from 3 institutions: DFCI (n = 187), MCC (n = 50) and MUHC (n = 65). Overall, 141 pts (46.7%) received Cisplatin/Gemcitabine, 130 (43.1%) received dose dense MVAC and the remaining received other regimens. The overall pCR rate was 26.2%. The 5-year OS was 62%. 63 (20.9%) pts were receiving an ACEi and 41 (13.6%) were receiving an ARB. ACEi prior to NAC approached significance for association with pCR (odds ratio = 1.71 (95% CI = 0.94-3.11) p = 0.077). Pts with cT3/4N0-N1 disease receiving ACEi had higher pCR rates (30.8% (8/26) vs 17.7% (14/98), p = 0.056) than those not on ACEi; no difference was observed for pts with cT2N0 tumors (31.1% vs 31.3%, p = 0.99). pCR, ECOG-PS and clinical stage were significantly associated with improved OS. ARB intake was not associated with pCR or OS. **Conclusions:** ACEi intake appeared potentially associated with increased pCR in pts with MIBC receiving NAC, which was more pronounced in those with higher clinical stages cT3/4N0-1. Given the association of pCR with OS, our data suggest the potential relevance of angiotensin as a therapeutic target in aggressive MIBC. Future prospective validation is warranted to repurpose angiotensin inhibitors in this setting, given their excellent toxicity profile and low costs. Research Sponsor: None.

Avelumab first-line (1L) maintenance + best supportive care (BSC) versus BSC alone in Asian patients with advanced urothelial carcinoma (UC): JAVELIN Bladder 100 subgroup analysis.

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Background: In the phase 3 JAVELIN Bladder 100 trial (NCT02603432), avelumab 1L maintenance therapy + BSC showed significantly longer overall survival (OS) vs BSC alone in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy. We report efficacy and safety results in patients enrolled in Asia. **Methods:** Patients with unresectable locally advanced or metastatic UC without disease progression after 4-6 cycles of gemcitabine + cisplatin or carboplatin were randomized 1:1 to receive avelumab 1L maintenance + BSC or BSC alone, stratified by best response to 1L chemotherapy and visceral vs nonvisceral disease when initiating 1L chemotherapy. The primary endpoint was OS, assessed from randomization in all patients and patients with PD-L1+ tumors (Ventana SP263 assay). **Results:** 147 Asian patients were enrolled at sites in Japan, South Korea, Taiwan, Hong Kong, and India; 73 and 74 were randomized to receive avelumab + BSC or BSC alone, respectively. Median OS (95% CI) was 25.3 mo (18.6 mo-not estimable [NE]) with avelumab+ BSC vs 18.7 mo (12.8 mo-NE) with BSC alone (HR, 0.74 [95% CI, 0.434-1.260]) in all patients, and 26.1 mo (18.2 mo-NE) vs 19.4 mo (11.9 mo-NE), respectively (HR, 0.66 [95% CI, 0.279-1.541]), in the PD-L1+ subgroup (n = 71). With avelumab + BSC vs BSC alone, median (95% CI) progression-free survival was 5.6 (2.0-7.5) vs 1.9 (1.9-1.9) months (HR, 0.58 [95% CI, 0.383-0.864]) in all patients and 6.8 (1.9-11.2) vs 1.9 (1.9-3.8) months (HR, 0.63 [95% CI, 0.336-1.172]) in the PD-L1+ subgroup; objective response rates (95% CI) were 9.6% (3.9%-18.8%) vs 2.7% (0.3%-9.4%) and 12.5% (4.2%-26.8%) vs 3.2% (0.1%-16.7%), respectively. The most common treatment-emergent adverse events (TEAEs) of any grade (any causality) in the avelumab + BSC arm were pyrexia (23.6%), constipation, nasopharyngitis, and rash (19.4% each); grade ≥3 TEAEs were anemia (9.7%), amylase increased (5.6%), and urinary tract infection (4.2%). **Conclusions:** Efficacy and safety data support the use of avelumab 1L maintenance as the standard of care in Asian patients with advanced UC that has not progressed with 1L platinum-based chemotherapy. Clinical trial information: NCT02603432. Research Sponsor: Pfizer., Pharmaceutical/Biotech Company.

Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Long-term follow-up results from the JAVELIN Bladder 100 trial.

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Background: The phase 3 JAVELIN Bladder 100 trial (NCT02603432) showed significantly longer overall survival (OS) with avelumab + best supportive care (BSC) vs BSC alone in patients (pts) with advanced UC that had not progressed with 1L platinum-containing chemotherapy. Avelumab 1L maintenance is now considered standard of care in treatment guidelines. We report trial data with ≥2-years follow-up in all pts (additional 19 months from the initial analysis). **Methods:** Pts with unresectable locally advanced or metastatic UC without disease progression with 4-6 cycles of 1L gemcitabine + cisplatin or carboplatin were randomized 1:1 to receive avelumab + BSC or BSC alone. The primary endpoint was OS, assessed from randomization in all pts and in pts with PD-L1+ tumors (Ventana SP263 assay). Secondary endpoints included progression-free survival (PFS) and safety. **Results:** 700 pts were randomized (350 per arm); 358 (51.1%) had PD-L1+ tumors. With extended follow-up (median, ≥38 months in both arms for all pts; data cutoff, June 4, 2021), OS remained significantly longer in the avelumab + BSC vs BSC alone arm in all randomized pts and in pts with PD-L1+ tumors (Table). An OS benefit was observed across prespecified subgroups. PFS (by investigator) was longer with avelumab + BSC vs BSC alone in all randomized pts and in pts with PD-L1+ tumors (Table). In the avelumab + BSC and BSC alone arms, respectively, 185 (52.9%) vs 252 (72.0%) pts received a subsequent anticancer drug therapy, including a PD-(L)1 inhibitor in 40 (11.4%) vs 186 (53.1%) pts. Long-term safety was consistent with previous avelumab monotherapy studies, with no new safety signals. **Conclusions:** Long-term follow-up from the JAVELIN Bladder 100 trial continues to show prolonged OS with avelumab + BSC vs BSC alone. These results further support the standard-of-care role for avelumab as 1L maintenance in pts with advanced UC that has not progressed with 1L platinum-containing chemotherapy. Clinical trial information: NCT02603432. Research Sponsor: Pfizer., Pharmaceutical/Biotech Company.

	All pts		Pts with PD-L1+ tumors	
	Avelumab + BSC (n = 350)	BSC alone (n = 350)	Avelumab + BSC (n = 189)	BSC alone (n = 169)
Median OS (95% CI), months	23.8 (19.9-28.8)	15.0 (13.5-18.2)	30.9 (24.0-39.8)	18.5 (14.1-24.2)
HR for OS (95% CI); 2-sided p value	0.76 (0.631-0.915); p = 0.0036		0.69 (0.521-0.901); p = 0.0064	
30-month OS rate, % (95% CI)	43.7 (38.2-49.0)	33.5 (28.4-38.7)	51.3 (43.7-58.4)	38.5 (30.9-46.1)
Restricted mean survival time (95% CI), months; 2-sided p value	28.8 (26.6-31.0); p = 0.0029	24.1 (21.9-26.3)	32.4 (29.4-35.4) p = 0.0080	26.4 (23.2-29.7)
Median PFS by investigator (95% CI), months	5.5 (4.2-7.2)	2.1 (1.9-3.0)	7.5 (5.5-11.1)	2.8 (2.0-3.7)
HR for PFS (95% CI); 2-sided p value	0.54 (0.457-0.645); p < 0.0001		0.46 (0.360-0.588); p < 0.0001	
30-month PFS rate, % (95% CI)	19.3 (15.0-24.0)	6.3 (3.8-9.5)	25.1 (18.6-32.2)	6.7 (3.3-11.6)

VAX014 for instillation in subjects with nonmuscle-invasive bladder cancer.

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Background: VAX014 is a novel tumor targeted oncolytic agent for intravesical administration. It is comprised of recombinant bacterial minicells, that actively target a3b1 and a5b1 integrins expressed on NMIBC and deliver an active cytotoxic/oncolytic protein payload, perfringolysin O. VAX014 is being investigated for the intravesical treatment of NMIBC in an ongoing multi-center Phase 1 marker lesion trial in subjects with low grade Ta disease (NCT 03854721). **Methods:** Subjects with up to 5 pathologically confirmed TaG1 lesions $\geq$ 5mm but $\leq$ 15mm are eligible to receive six (6) weekly intravesical instillations of VAX014. Subjects with presence or history of high-grade bladder cancer are ineligible. Phase 1a will establish the MTD using a 3+3 design. After the DSMB establishes the RP2D, a Phase 1b expansion will use this dose to treat an additional 10 patients. **Results:** No serious adverse events or dose limiting toxicities have been recorded through two dose cohorts (3 + 3 design) and evidence of clinical response has been observed. Treatment related adverse events have been limited to Grade 1/2 hematuria, dysuria, and urgency. Preclinical studies indicate the pharmacodynamic activity of VAX014 following weekly intravesical administration to immune competent mice bearing bladder tumors is immune dependent and synergizes with systemic PD-L1 blockade to eliminate organ confined tumors and extravesical tumors. Surviving mice are capable of rejecting tumor rechallenge due to development of protective antitumor immunologic memory in response to therapy. Exploratory immunohistochemical target validation studies in bladder tumor biopsy specimens from subjects with more advanced stage tumors (T1-T3), indicate overexpression of VAX014's target integrins, a3b1 and a5b1, in most samples tested. **Conclusions:** These clinical and preclinical data support the further development of VAX014 for the intravesical treatment of NMIBC and set a foundation for combination therapy with systemically administered immune checkpoint blockade in subjects with advanced disease. Clinical trial information: NCT03854721. Research Sponsor: Vaxiion Therapeutics, U.S. National Institutes of Health.

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Reduction of residual tumors by photodynamic diagnosis-assisted TURBT using 5-aminolevulinic acid for high-risk nonmuscle-invasive bladder cancer (BRIGHT study).

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Background: High-risk non-muscle invasive bladder cancer (NMIBC) has high tumor residual rate of 40–60% after TURBT, and second TUR is strongly recommended. Photodynamic diagnosis-assisted TURBT (PDD-TURBT) using 5-aminolevulinic acid (5-ALA) has been reported to reduce residual tumors and intravesical recurrence. The purpose of this study is to investigate the residual tumor-reducing effect of PDD-TURBT for high-risk NMIBC and to explore the possibility that second TUR could be omitted by PDD-TURBT. **Methods:** We conducted an investigator-initiated multicenter prospective observational study (BRIGHT study; UMIN000035712) involving patients who underwent PDD-TURBT using 5-ALA and second TUR for high-risk NMIBC (high-grade UC or pT1 or concurrent CIS). The primary endpoint was tumor residual rate and the secondary endpoint was recurrence-free survival, which were compared with historical data (conventional TURBT) using propensity score-matching (PSM; caliper: 0.2). Assuming that the difference between the two groups was 20%, the planned number of cases was statistically set to 200 PDD-TURBT cases and 300 historical data cases, and the registration period was 2 years from January 2019 to December 2020, and the follow-up period was 2 years after second TUR. **Results:** In this study, 188 patients in the PDD-TURBT group and 313 patients in the historical group were enrolled, and 177 patients and 306 patients were included in the final analysis, respectively. After PSM adjustment, 167 patients in both groups were compared, and no significant differences were observed in age, gender, history of bladder cancer, tumor diameter, number of tumors, history of upper tract urothelial cancer, and period from initial TURBT to second TUR. The tumor residual rate was 25.8% in the PDD-TURBT group compared with 47.3% in the historical group, showing a significant decrease (odds ratio 0.39 [95% CI: 0.24–0.63]; p = 0.000064). Logistic regression analysis revealed that significant factors predicting residual tumors in PDD-TURBT were current or past smoking history, multiple tumors, and non-pTa (pT1 or pTis) tumors. Focusing on these three factors, patients with 0–1 of these three factors have a significant less tumor residual rate compared with patients with 2–3 factors (8.33% vs. 33.3%; odds ratio 5.46 [95% CI: 1.81–22.3]; p = 0.00052). **Conclusions:** PDD-TURBT for high-risk NMIBC significantly reduced the tumor residual rate at the second TUR compared to the conventional TURBT. PDD-TURBT using 5-ALA may enable to omit second TUR in some high-risk NMIBC cases. Clinical trial information: UMIN000035712. Research Sponsor: Chugai Pharmaceutical Co., Ltd., Pharmaceutical/Biotech Company.

Phase I-II study to evaluate safety and efficacy of niraparib plus cabozantinib in patients with advanced urothelial/kidney cancer (NICARAGUA trial): Preliminary data of phase I study.

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Background: Niraparib (N) is a (PARP)-1/-2 inhibitor and Cabozantinib (C) is a tyrosine kinase (TK) inhibitor that targets VEGF signalling via inhibition of multiple TK receptors including c-MET and TAM kinases (TYRO3, AXL, MER). The c-Met receptor TK is abnormally activated and could be decrease response to PARP inhibitors. Preclinical data reveals that treatment with c-Met inhibitors renders cells more sensitive to PARP inhibition. A phase (Ph) I-II study was designed to explore the safety and efficacy of the combination of N + C in genitourinary cancers. **Methods:** Multicenter, open-label Ph I-II study (NCT03425201). Confirmed histopathological diagnosis of either metastatic urothelial carcinoma (mUC) or advanced clear cell renal cell carcinoma previously treated with a maximum of two previous regimens. Adequate bone marrow, liver and renal functions were required. The Ph I portion aimed to identify the maximum tolerated dose (MTD) and recommended ph II dose (RP2D). Pt received N and C p.o. once daily in 28-day cycles: Dose level 1 (DL1) N/C 100/20 mg; DL2 200/20 mg; DL3 200/40 mg; DL4 200/60 mg. A further amendment developed DL1.1 100/40 mg. Pt were accrued to each dose level in cohorts of 6 pt until the MTD was achieved (defined as highest dose at which ≤ 1 out of 6 pt experience a DLT, evaluated during the first 2 cycles). **Results:** Nineteen evaluable pt for DLT were included, 14 of them had UC. There was no DLT at DL1. Two out of the first 6 evaluable pt in DL2 had DLT (G3 thrombopenia and anemia and G3 diarrhea respectively). Upon analysis of these pt it was agreed to include 3 additional new pt for evaluation. Two pt were included with one presenting a DLT (G3 hepatic toxicity). Enrolment then continued in a new DL 1.1 cohort and 1 of 6 pts had DLT (G3 mucositis), being then considered the RP2D. No toxic deaths were reported. Six pt (32%) received at least 10 cycles and 9 pt (47%) received at least 6 cycles. Three patients (16%) achieved partial response (all of them with mUC disease) and 14 (74%) stable disease. **Conclusions:** N plus C combination can be safely administered with a manageable toxicity profile and preliminary efficacy was reported in mUC heavily pretreated pts. The RP2D is N 100 mg plus C 40 mg qd. Ph II study is now recruiting mUC patients. Clinical trial information: NCT03425201. Research Sponsor: GSK; IPSEN.

Planned dose levels for phase I.

Dose Level	Niraparib (mg)	Cabozantinib (mg)
DL1	100	20
DL1.1	100	40
DL2	200	20
DL3	200	40
DL4	200	60

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Analysis of disease-free survival in CheckMate 274 by PD-L1 combined positive score and tumor proportion score.

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Background: CheckMate 274 demonstrated a significant improvement in disease-free survival (DFS) with nivolumab (NIVO) versus placebo (PBO) both in the intent-to-treat population (hazard ratio [HR], 0.70; 98.22% confidence interval [CI], 0.55–0.90; $P < 0.001$) and in patients (pts) with tumor programmed death ligand 1 (PD-L1) expression ≥ 1% assessed by the tumor proportion score (TPS) (HR, 0.55; 98.72% CI, 0.35–0.85; $P < 0.001$). An exploratory subgroup analysis showed a trend toward a DFS benefit with NIVO in pts with TPS < 1% (0.82; 95% CI, 0.63–1.06). To further characterize the relationship between PD-L1 expression and NIVO efficacy, we report an analysis of DFS based on PD-L1 expression in both tumor and immune cells using the combined positive score (CPS). **Methods:** CheckMate 274 is a phase 3, randomized, double-blind, multicenter trial of NIVO versus PBO in pts with high-risk muscle-invasive urothelial carcinoma after radical surgery. Pts were randomized 1:1 to NIVO 240 mg or PBO every 2 weeks intravenously for 1 year of adjuvant treatment. The primary endpoints of the study are DFS in the intent-to-treat population and in pts with TPS ≥ 1%. The Dako PD-L1 IHC 28-8 pharmDx assay was used to evaluate TPS. CPS was determined retrospectively from previously stained immunohistochemistry slides using the CPS algorithm. CPS was calculated as the number of both PD-L1 positive tumor and immune cells divided by the number of viable tumor cells in the evaluable tumor area, multiplied by 100; TPS was similarly calculated with the number of PD-L1 positive tumor cells as the numerator. This analysis only included pts with both quantifiable CPS and TPS. **Results:** Of the 629 pts with quantifiable TPS and CPS, 249 (40%) had TPS ≥ 1% (NIVO, n = 124; PBO, n = 125), 380 (60%) had TPS < 1% (NIVO, n = 191; PBO, n = 189), 557 (89%) had CPS ≥ 1 (NIVO, n = 281; PBO, n = 276), and 72 (11%) had CPS < 1 (NIVO, n = 34; PBO, n = 38). Within TPS < 1% pts, 81% (n = 309) had CPS ≥ 1. The number of pts and the DFS outcomes in pts with TPS ≥ 1% and CPS ≥ 1 are shown in the Table. In pts with TPS < 1% who also had CPS ≥ 1, median DFS (95% CI) was 19.2 (15.6–33.4) months with NIVO versus 10.1 (8.2–19.4) months with PBO. The HR for NIVO versus PBO in these pts was 0.73 (95% CI, 0.54–0.99). **Conclusions:** This exploratory analysis of PD-L1 expression by CPS showed a higher proportion of pts with CPS ≥ 1 than TPS ≥ 1%, and that most pts with TPS < 1% had CPS ≥ 1. In the CPS ≥ 1 subgroup, median DFS with NIVO was more than double that with placebo. These results support the conclusion that pts with TPS < 1% also benefit from adjuvant NIVO. Clinical trial information: NCT02632409. Research Sponsor: Bristol Myers Squibb.

		Median DFS (95% CI), mo	HR (95% CI)	6-mo DFS probability, %	12-mo DFS probability, %
TPS ≥ 1%	NIVO (n = 124)	NR (24.6–NE)	0.50 (0.35–0.71)	75	69
	PBO (n = 125)	8.4 (5.6–17.9)		56	45
CPS ≥ 1	NIVO (n = 281)	24.6 (19.2–NE)	0.62 (0.49–0.78)	77	67
	PBO (n = 276)	9.4 (8.2–15.2)		60	46

NE, not estimable; NR, not reached.

CIMUC: Chemotherapy following Immune checkpoints inhibitors in patients with locally advanced or metastatic urothelial carcinoma (la/mUC).

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Background: Immune checkpoints inhibitors (ICIs) have recently changed therapeutic landscape of la/mUC. Recent studies suggested an improvement of response to salvage chemotherapy (CT) after ICIs in several cancer types including urothelial carcinoma. We assumed that efficacy of CT rechallenge after ICIs may be improved compared to second-line CT without previous ICIs in patients (pts) with la/mUC. **Methods:** CIMUC is a French multicentric retrospective study including all pts with la/mUC initiating second or third-line CT from January 1st 2015 to June 30th 2020. Two groups of pts were defined: pts in group 1 (G1) were treated with a second-line CT without previous ICIs; pts in group 2 (G2) were treated with third line CT after ICIs. Primary endpoint was objective response rate (ORR: proportion of patients with complete or partial response, according to RECIST 1.1 criteria) in G2 *versus* G1. Secondary endpoints were progression-free survival (PFS), defined as time from initiation of second or third-line CT to disease progression or death from any cause, and toxicities. This study is supported by the French Genito Urinary Group (GETUG). **Results:** 553 pts were included. Baseline characteristics of the 2 groups are summarized in the Table. ORRs were 31% (95%CI [26.5-35.5]) and 29.2% (95%CI [21.9-36.6]) respectively in G1 and G2, without statistically significant difference (p=0.617), even after adjustment for Bellmunt risk factors (p=0.3214). In subgroups analysis, no difference in ORR was observed by type of CT (platinum or taxanes), duration of response (DOR) to first-platinum-based CT (< 12 months or ≥ 12 months) and FGFR-status. We did not identify any predictive factor of OR in G2 in multivariate analysis. Median PFS were 4.6 months (95%CI [3.88; 5.06]) and 4.86 months (95%CI [4.11; 5.45]), respectively in G1 and G2. Grade 3/4 hematologic toxicity occurred in 35% and 22.4%, respectively in G1 and G2. **Conclusions:** While ORR was not superior in G2 versus G1, pts derive comparable benefit in a further line of treatment (G2) in terms of ORR and PFS. Despite limits inherent to any retrospective study, CIMUC represents one of the largest retrospective studies in this setting. Research Sponsor: None.

Baseline characteristics of patients included in CIMUC study (n=553).

	Group 1 (CT-> CT) (N=406)	Group 2 (CT-> ICI -> CT) (N=147)
Age (median [IQR])	66.3 [60.2-73.6]	69.9 [62.6-74.0]
ECOG PS (n (%)) 0 1 ≥ 2 Unknown	70 (17.2) 204 (50.2) 128 (31.5) 4 (1.0)	49 (33.3) 78 (53.1) 15 (10.2) 5 (3.4)
Bellmunt factors (n (%)) 0 1 2 3 Unknown	39 (9.6) 177 (43.6) 143 (35.2) 43 (10.6) 4 (1.0)	28 (19.0) 75 (51.0) 36 (24.5) 2 (1.4) 6 (4.1)
Chemotherapy (n (%)) Taxane Platinum Other Unknown	130 (32.0) 209 (51.5) 66 (16.3) 1 (0.2)	74 (50.3) 48 (32.7) 25 (17.0) 0 (0.0)
FGFR status (n (%)) Altered Non-altered Unknown	16 (3.9) 62 (15.3) 328 (80.8)	10 (6.8) 39 (26.5) 98 (66.7)
DOR ≥ 12 months to first platinum based therapy (n (%))	115 (28.3)	23 (15.6)

Atezolizumab (atezo) with or without Bacille Calmette-Guérin (BCG) in patients (pts) with high-risk nonmuscle-invasive bladder cancer (NMIBC): Results from a phase Ib/II study.

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Background: Standard treatment (tx) for high-risk NMIBC is transurethral resection of bladder tumor (TURBT) followed by BCG induction and maintenance. However, ≈50% of pts experience recurrence and/or progression after tx and may be ineligible for or refuse cystectomy. The PD-L1/PD-1 pathway may be involved with immune escape in NMIBC following BCG exposure. Here, we report results of atezo (antiPD-L1) ± BCG in BCG-unresponsive, high-risk NMIBC. **Methods:** This multicenter study (NCT02792192) enrolled pts with BCG-unresponsive NMIBC with carcinoma in situ who had repeat TURBT. Cohort 1A and 1B pts received atezo 1200 mg IV q3w for ≤96 wk. Cohort 1B pts also received standard BCG induction (qw × 6 doses) and maintenance (qw × 3 doses at 3 mo), with optional maintenance courses at 6, 12, 18, 24, and 30 mo. For cohort 1B only, de-escalation was allowed for ≤3 BCG dose levels (full dose 50 mg, 66% and 33% of full dose). Co-primary outcomes were safety and complete response (CR) rate at 6 mo (6-mo bladder biopsy required). Duration of CR and 3-mo CR rate (key secondary outcomes) and 12-mo CR rate (exploratory) were also shown. **Results:** Cohorts 1A and 1B enrolled 12 pts each. Median age was 74 y; most pts had ECOG PS 0 (n = 7 [58%] in each cohort). At data cutoff (Sep 29, 2020), median atezo tx duration was 22.7 wk in cohort 1A and 31.6 wk in 1B. Following dose de-escalation in cohort 1B, the recommended BCG dose was 50 mg. BCG dose modification/interruption occurred in 4 pts (33%) due to an AE. The most common reason for tx discontinuation was disease recurrence or progression in both cohorts. Three pts (25%) in cohort 1A had atezo-related Gr 3 AEs (most common: maculopapular rash, n = 2); no atezo- or BCG-related Gr ≥3 AEs were seen in cohort 1B. Three dose-limiting toxicities occurred (1 [8%] in cohort 1A and 2 [17%] in cohort 1B), all reported as AEs of special interest. No Gr 4/5 AEs were reported. CRs, which appeared durable, were seen in both cohorts (Table). **Conclusions:** In this first report of atezo + BCG in NMIBC, atezo as mono- and combination therapy was well tolerated, with no new safety signals or tx-related deaths. Preliminary data suggested clinically meaningful activity, especially with atezo + BCG, requiring confirmation in a larger setting. Clinical trial information: NCT02792192. Research Sponsor: F. Hoffmann La-Roche Ltd.

	Cohort 1A Atezo (n = 12)	Cohort 1B Atezo + BCG (n = 12)	Cohort 1 total (N = 24)
Best response, n (%)[a]			
CR	4 (33)	7 (58)	11 (46)
Persistent or recurrent disease	7 (58)	4 (33)	11 (46)
Progressive disease	0	1 (8)	1 (4)
3-mo CR rate, n (%) [95%CI]	2 (17) [2, 48]	5 (42) [15, 72]	7 (29) [13, 51]
6-mo CR rate, n (%) [95%CI]	4 (33) [10, 65]	5 (42) [15, 72]	9 (38) [19, 59]
12-mo CR rate, n (%) [95%CI]	1 (8) [0, 39]	5 (42) [15, 72]	6 (25) [10, 47]
Duration of CR (in pts with 6-mo CR), median (range), mo	6.8 (3.0-22.3*)	NE (13.8*-24.5*)	NE (3.1-24.5*)
No. of events, n (%)	2 (50)	0	2 (22)

* Censored. NE, not estimable. [a] Missing for 1 cohort 1A pt.

A prospective phase II trial of neoadjuvant nivolumab plus gemcitabine/cisplatin chemotherapy in muscle-invasive urothelial carcinoma of bladder.

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Background: To assess the efficacy and safety of the combination of nivolumab plus gemcitabine/cisplatin in neoadjuvant setting of muscle-invasive urothelial carcinoma of bladder (MIBC). **Methods:** In this prospective phase II trial (CRIS, KCT0003804), eligible patients had cT2-T4a N0 MIBC, cisplatin-eligible, and to be planned radical cystectomy. Patients received nivolumab 3 mg/kg on days 1 and 15, cisplatin 70 mg/m2 on day 1, and gemcitabine 1,000 mg/m2 on days 1, 8 and 15. Study treatment was repeated every 28 days up to 3 or 4 cycles, depending on the surgery schedules. The primary endpoint was pathologic complete response (pCR, ypT0). Secondary endpoints included pathologic downstaging (<ypT1), disease-free survival (DFS) and safety. **Results:** Between Sep 2019 and Oct 2020, 51 patients were enrolled. The majority of patients (96%) completed the planned (median, 3; range 1 to 4) cycles of nivolumab plus gemcitabine/cisplatin without significant toxicities. The most commonly observed adverse events included fatigue, nausea and pruritus. Among the 49 patients who completed study treatment, 12 patients refused surgery but were treated with concurrent chemoradiotherapy. Radical cystectomy was performed in 34 (69%) patients. Pathologic results revealed 12 pCR (ypT0, 35%), 4 ypTis, 3 ypTa, 3 ypT1, and 12 ypT2/T3. Preoperative PD-L1 (22C3 TPS>1%) did not correlate with pCR or pathologic downstaging rates. With a median follow-up of 19 months (95% CI, 17 to 20), 12 patients experienced disease recurrence and median DFS was not reached. **Conclusions:** Neoadjuvant nivolumab plus gemcitabine/cisplatin was feasible and provided meaningful pathologic responses in patients with MIBC. Clinical trial information: KCT0003804. Research Sponsor: hematoma@skku.edu.

495 **Poster Session**

Factors associated with improved outcomes in surgically resectable small cell urothelial cancer (SCUC).

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Background: We have established that neoadjuvant (neo) chemotherapy (CTX) is the optimal strategy in localized SCUC given the frequent under staging. We have also demonstrated that alternating ifosfamide/doxorubicin (IA) and etoposide/cisplatin (EP) are active against SCUC; however, the optimal regimen has not been defined. **Methods:** We reviewed the records of 410 patients with SCUC treated at our institution between 1985 and 2020. Fisher's exact test and logistic regression were used to determine the association between pathological complete response (pCR) and management approach. The Kaplan-Meier method was used to estimate overall survival (OS) from time of SCUC diagnosis to death or last follow up. Log rank test and Cox proportional models were used to determine the hazard-ratio (HR) between OS and management approach. **Results:** We included 203 patients with cT2-4aN0M0 SCUC who underwent cystectomy either after neoCTX (141, 69%), alone (38, 19%), or followed by adjuvant CTX (24, 12%). Clinical stage was cT2N0 (151, 74%), cT3/4N0 (44, 22%), or cTxN0 (8, 4%). Median age at diagnosis of SCUC was 66.7, 65.7, and 62.3 (p = 0.1) in the neoCTX, surgery alone and adjuvant CTX groups, respectively. Mean (+/- standard deviation) baseline glomerular filtration rate (GFR) was 75.6 (+/- 19.5), 61.3 (+/- 18.7), 70.5 (+/- 30.1) (p = 0.002) in the neoCTX, surgery alone and adjuvant CTX groups, respectively. Downstaging was significantly improved with neoCTX vs initial surgery (49.6% vs 14.5%, p <.0001), stage cT2N0 vs cT3/4N0 (44% vs 25%, p = 0.01), presence of carcinoma-in-situ (47% vs 28%, p = 0.01), or higher GFR (OR = 1.02, p = 0.06). In a multi-variable analysis of these factors, neoCTX was the only factor associated with pCR [OR = 3.9 (1.6-9.6) p = 0.003]. When comparing neoCTX regimens, downstaging was greatest with IA/EP (65%) as compared to EP (39%), MVAC/Gem/Cis (27%) or others (36%), p = 0.04. IA/EP was associated with younger age and good ECOG PS. In a multi-variable analysis of these factors, only IA/EP was associated with downstaging [OR = 3.7 (1.3-10.2), p = 0.01] and cT3/4 trended toward negatively impacting downstaging [OR = 0.5 (0.15-1.57), p = 0.23]. In the survival analysis, neoCTX, T2 vs T3/4, predominant small cell histology, good ECOG PS, higher GFR, and younger age were all significantly associated with improved outcomes. The best survival outcomes were observed with IA/EP (5-yr OS 64.2%), as compared to EP (5-yr OS 55.6%), MVAC/Gem/Cis (5-yr OS 50%) or others (5-yr OS 46.4%), p = 0.06, although these findings did not achieve statistical significance. **Conclusions:** NeoCTX remains the standard of care treatment for SCUC. The best downstaging was observed with IA/EP with a trend toward improved overall survival. We recommend the use of IA/EP whenever possible and consider EP for patients who are not able to tolerate ifosfamide. Research Sponsor: None.

Sequential intravesical valrubicin and docetaxel for the treatment of nonmuscle invasive bladder cancer.

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Background: Intravesical gemcitabine-docetaxel (Gem/Doce) has emerged as an efficacious and well-tolerated therapy for NMIBC. At first cytoscopic evaluation, success rate for BCG failures is 75-80% with 60% of responders remaining disease free at 24 months. Success rates are even higher for BCG naïve patients with close to 90% disease free at 3 months, and 93% of responders HG disease free at 24 months. There is an unmet need for effective bladder-sparing regimens for Gem/Doce failures. FDA-approved agents in this setting have poor long-term efficacy; Valrubicin has an 8% 24-month disease free rate, and recently approved Pembrolizumab has less than 20% complete response at 1 year. Based on poor efficacy of alternatives, we evaluated sequential intravesical valrubicin-docetaxel (Val/Doce) as a rescue therapy for NMIBC. **Methods:** We retrospectively identified all patients with NMIBC who were treated with Val/Doce between April 2013 and June 2021. Patients were included with intent to receive 6 weekly intravesical instillations of sequential 800 mg valrubicin and 37.5 mg docetaxel after complete TURBT. Monthly maintenance of 2 years was initiated if disease free at 3-month cytoscopic evaluation. The primary outcome was recurrence-free survival (RFS). Progression events included the development of muscle invasive or metastatic disease as well as any cystectomy. Survival was assessed using the Kaplan-Meier method and log rank test, indexed from start of Val/Doce induction. Surveillance was performed according to AUA guidelines. **Results:** The final cohort included 75 patients with median follow-up of 21 months. Of these patients, 12 were treated with Val/Doce for low-grade Ta disease, with 60% disease free at 2 years and no subsequent HG occurrences. The remaining 63 patients had high-grade disease of which 86% were BCG failures and 89% were Gem/Doce unresponsive. The 2 year RFS for high-grade patients was 39%. CIS was present in 56% of the cohort. RFS was similar for those with and without CIS. Progression occurred in 12 of the patients with high-grade disease. Of note, 10 underwent cystectomy and 2 died of metastatic bladder cancer, yielding a bladder cancer specific death rate of 3%. Overall and cystectomy-free survival was 88 and 85% at 24 months, respectively. The most commonly reported side effects were bladder spasms (24%), urinary frequency (13%), and dysuria (11%). There were 3 patients who could not tolerant a full induction course. **Conclusions:** Sequential intravesical valrubicin-docetaxel will rescue a substantial portion of patients with HG NMIBC failing Gem/Doce or BCG. Thus, the regimen allows a high proportion of patients ($>$ 80%) to retain their bladders with an acceptable ($<$ 20%) progression rate without succumbing to bladder cancer-related death ($<$ 5%). Research Sponsor: John & Carol Walter Family Foundation and the Carver College of Medicine.

Variable	6 Months	12 Months	24 Months
HG RFS for CIS Containing	61%	53%	36%
HG RFS for Ta/T1 HG	69%	63%	39%
Progression-Free Survival	90%	85%	83%

Sequential intravesical gemcitabine and docetaxel for BCG-naïve high-risk nonmuscle-invasive bladder cancer.

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Background: Bacillus Calmette-Guerin (BCG) is currently recommended as adjuvant therapy following complete transurethral resection of bladder tumor (TURBT) for high-risk non-muscle invasive bladder cancer (NMIBC). However, continued BCG production shortages have precluded the use of BCG in many urologic practices. Efficacy of sequential intravesical gemcitabine and docetaxel (Gem/Doce) in the BCG failure setting has been reproduced across multiple institutions. In response to the continuing BCG shortage, Gem/Doce has been utilized at our institution in the BCG-naïve setting. We report the outcomes of a large cohort of patients with high-risk BCG-naïve NMIBC treated with Gem/Doce. **Methods:** We retrospectively identified all patients with BCG-naïve high-risk NMIBC who were treated with Gem/Doce from May 2013 through April 2021. We included patients with intent to receive 6 weekly intravesical instillations of sequential 1 gram gemcitabine and 37.5mg docetaxel after complete TURBT. Monthly maintenance of 2 years was initiated if disease free at first follow-up. The primary outcome was recurrence-free survival (RFS) and efficacy was evaluated in an intention-to-treat manner. Recurrence was defined as pathologically confirmed tumor relapse in the bladder or prostatic urethra. Progression was defined as T-stage increase from Ta or CIS to T1 or development of muscle invasive or metastatic disease. Survival was assessed using the Kaplan-Meier method and log rank test, indexed from the first Gem/Doce instillation. **Results:** One hundred seven patients with median follow-up of 15 months were included in the analysis. There were 47 with any CIS, 55 with T1 disease, and 7 with micropapillary variant histology. Four patients did not complete a full induction cycle due to hematuria (3) and severe frequency/nocturia (1). 19 patients sustained a recurrence at any point during follow-up. RFS was 89%, 85%, and 82% at 6, 12, and 24 months, respectively. No difference in RFS was seen in patients with or without CIS ($p = 0.42$). No patients met criteria for either form of disease progression. One patient underwent cystectomy due to end-stage lower urinary tract symptoms, with final pathology pTisN0. No patients died of bladder cancer. Overall survival was 84% at 24 months. 46 patients reported any symptoms during treatment. Common side effects included urinary frequency/urgency (36%), hematuria (11%), and dysuria (8%). **Conclusions:** In a large cohort of high-risk, BCG-naïve NMIBC patients, Gem/Doce showed excellent efficacy (84% 2-year HG-RFS). These rates are similar to modern treatment naïve cohorts receiving BCG. Prospective comparative analysis of Gem/Doce in BCG-naïve populations is warranted. Research Sponsor: John & Carol Walter Family Foundation and the Carver College of Medicine.

Variable	6 Months	12 Months	24 Months
Recurrence-Free Survival	89%	85%	82%
High-Grade Recurrence-Free Survival	91%	87%	84%
Overall Survival	98%	98%	84%

Neoadjuvant nivolumab (N) +/- ipilimumab (I) in cisplatin-ineligible patients (pts) with muscle-invasive bladder cancer (MIBC).

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Background: Cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy (RC) confers survival benefit but a substantial subset of MIBC pts are cisplatin-ineligible. We conducted a phase II trial of N±I neoadjuvant therapy for cisplatin-ineligible MIBC. **Methods:** Cisplatin-ineligible pts with MIBC (cT2-T4aN0M0) were enrolled into 2 consecutive cohorts of 15 pts each (C1: N 3 mg/kg q 2 weeks (wk) x 5; C2: I (3mg/kg) + N (1mg/kg) wk 0 and 6, with N (3mg/kg) wk 3 and 9). A 3rd cohort was planned (C3: I (3mg/kg) + N (1mg/kg) q 3 wk x 3). Primary endpoint (EP) was eligibility for planned RC within 60 days without delay from treatment-related adverse events (TRAEs) or progressive disease (PD). Secondary EPs included pathologic downstaging (PaDo, <ypT2pN0) and complete response (pCR, ypT0pN0) rates, recurrence-free survival (RFS), and safety. Exploratory EP was event-free survival (EFS). **Results:** From 8/2018-5/2021, 15 pts were enrolled onto C1 and C2 (N = 30). Median age 76 (range 53-87), 80% male, with median Charlson comorbidity score of 1 (range 0-5). In C1 and C2, 14/15 and 6/15 pts received all planned treatment, respectively. In C2, 7/15 received ≤ 50% of planned doses. In C1, 11 pts underwent RC, 2 had PD before RC, 1 did not undergo RC due to TRAE, and 1 declined RC. Overall, 12/15 met the primary EP. For C2, 9 pts underwent RC, 3 had PD before RC, 2 did not undergo RC due to AE (1 of which was TRAE), and 1 opted for radiation, with 8/15 meeting the primary EP. C3 was dropped due to C2's failure to meet the primary EP. In C1, 4 pts had PaDo (26%), with 2 pCRs (13%). In C2, 3 pts had PaDo (20%), with 1 pCR (7%). In C1, 1 pt who did not undergo RC due to TRAE had clinical CR of 13.2 months (mos) but died of sepsis at 16.1 mos; 2 pts in C2 who did not undergo RC have ongoing clinical CR at 16.1 and 10.8 mos follow-up (f/u). For time-to-event EPs, see Table. In C1, the only observed grade 3-4 TRAE was myocarditis (n=1, 7%). In C2, 4 pts (27%) had grade 3-4 TRAE, including elevated lipase (20%), pneumonitis (13%), fatigue (13%), and elevated AST + ALT(13%). Median tumor mutation burden was 8.8/megabase; DNA damage response genes were altered in 31% of pts and FGFR3 in 14%, with no genomic correlation with PaDo. For C1, 4/10 had baseline PD-L1 expression on ≥1% of tumor cells; 1 had PD-L1 ≥5%. **Conclusions:** In this cohort of cisplatin-ineligible pts with MIBC and comorbidities, neoadjuvant N was well tolerated. N+I was associated with greater toxicity resulting in RC delays. Pathologic response rates were low in both cohorts, raising questions about utility of treatment intensification in cisplatin-ineligible patients. Some pts who did not undergo RC due to TRAEs had sustained clinical CR. Clinical trial information: NCT03520491. Clinical trial information: NCT03520491. Research Sponsor: Bristol Myers Squibb., Conquer Cancer Foundation of the American Society of Clinical Oncology., U.S. National Institutes of Health.

	Cohort 1	Cohort 2
Median f/u (mos)	27	8
6mos RFS	86%	68%
95% Confidence Interval (95CI)	69 - 100	47 - 100
12mos RFS	77%	68%
95CI	57 - 100	47 - 100
6mos EFS	92%	79%
95CI	77 - 100	60 - 100
12mos EFS	81%	79%
95CI	61 - 100	60 - 100

499 **Poster Session**

Real-world study of chemotherapy plus immunotherapy versus chemotherapy alone as neoadjuvant treatment guided bladder-sparing therapy for localized muscle-invasive bladder cancer.

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Background: Bladder-preserving combined-modality therapy has been a popular research field as an alternative to radical cystectomy for selected patients with localized muscle-invasive bladder cancer (MIBC). This real-world study aimed to compare the efficacy of neoadjuvant chemotherapy plus immunotherapy versus chemotherapy alone as one of bladder-sparing therapies for localized MIBC. **Methods:** Patients with cT2-4bN0-3M0-1a pathological and imaging diagnosed MIBC were included in the study. Either chemotherapy (gemcitabine and cisplatin/carboplatin) plus immunotherapy (PD-1 checkpoint inhibitor, including pembrolizumab , tislelizumab and toripalimab) or chemotherapy alone were given as patients' wish. The primary endpoint was complete response rate (CR, T0/Ta/Tis), and the secondary endpoints were disease control rate (DCR), progression-free survival (PFS), bladder-intact disease-free survival (BI-DFS) and toxicity. **Results:** In total, 41 patients were included, 25 in combination group and 16 in chemotherapy group respectively. The baseline characteristics were well balanced in two groups. Median follow-up time was 15.3 ±4.4 months(m). No patient died. The efficacy evaluable population was consisted of 34 pts (22 in combination group; 12 in chemotherapy alone group). The CR rate for combination group was 50.0% and 0 for chemotherapy alone group. One patient suffered from disease progression in combination group and three in chemotherapy group. The DCRs for combination group and chemotherapy group were 95.5% and 66.7%, respectively (p= 0.003). Twelve patients had radiotherapy and six patients had radical cystectomy followed by neoadjuvant treatments in combination group. And two patients had radiotherapy and three patients had radical cystectomy in chemotherapy group. The one-year PFS rates were 95.5% and 62.5% for combination group and chemotherapy group(p= 0.010), and the one-year BI-DFS were 66.1% versus 27.5% respectively(p= 0.159). The bladder-preserving combined-modality therapies used were well-tolerated with acceptable and manageable toxicities. Grade ¾ hematological system adverse events were 15.9% and 6.4% in combination group and chemotherapy group, respectively (p= 0.021). **Conclusions:** Neoadjuvant chemotherapy plus immunotherapy showed better efficacy compared with chemotherapy alone as an important bladder-sparing therapy for locally advanced MIBC with acceptable and manageable toxicities. Research Sponsor: None.

500 **Poster Session**

Gemcitabine and carboplatin versus gemcitabine and paclitaxel chemotherapy in cisplatin ineligible advanced-stage urothelial cancers: A prospective randomized control study.

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Background: Cisplatin ineligibility in metastatic urinary bladder cancer patients poses a major therapeutic challenge. The reported incidence was approximately 20-30% of metastatic urinary bladder cancer. In the absence of insurance, "the immunotherapy" can be economically draining at the current cost. Moreover, there are patients in whom immunotherapy might not be feasible due to comorbid conditions. Therefore, there persists a need to optimize chemotherapy options for gemcitabine combination with either Paclitaxel or Carboplatin are recommended chemotherapy options. However, limited prospective studies are comparing the two options. **Methods:** This was a non-funded, prospective, randomized, single-center study among treatment naïve cisplatin-ineligible metastatic urothelial cancer from a tertiary care institute from India. The study enrollment duration was 18 months. Patients were randomized in one of the two treatment arms. The "Arm A" received (Gemcitabine and Carboplatin) and "Arm B" received the (Gemcitabine and Paclitaxel) combination chemotherapy, respectively. The two treatment arms were compared prospectively for disease control, survival, and adverse events in an Intention to treat analysis. **Results:** A total of 32 eligible participants were randomized in the study. "Arm A" vs. "Arm B" had an 18.7% vs. 25% drops out rate, respectively. The ORR was 40% vs. 88.4%; median PFS and OS were 3.7 vs. 3.8 months and 7.3 vs. 14.0 months, respectively. The serious adverse events were nonoverlapping. Hospitalization was needed for the care of adverse events among 37.5% vs. 12.5% patients, respectively. **Conclusions:** Both groups reported that similar PFS. However, better ORR, OS (though not statically significant), and lower hospitalizations for adverse event management favor the Gemcitabine with paclitaxel combination over Gemcitabine with Carboplatin. Clinical trial information: CTRI/2020/02/023402. Research Sponsor: None.

501 **Poster Session**

Futibatinib plus pembrolizumab in patients (pts) with advanced or metastatic urothelial carcinoma (mUC): Preliminary safety results from a phase 2 study.

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Background: Immune checkpoint inhibitors (ICIs), including pembrolizumab, are among the few treatment options available for platinum-ineligible pts with mUC, but only 25–30% of pts achieve responses with ICIs. *FGFR* DNA alterations (in 15–20% of mUCs) may contribute to poor responses to ICIs, and FGFR inhibition may sensitize tumors to ICIs by direct action on cancer cells or by altering the tumor microenvironment. In an open-label phase 2 study (NCT04601857), futibatinib, a highly selective, potent, irreversible FGFR1–4 inhibitor with activity in FGFR-deregulated tumors, is being assessed in combination with pembrolizumab in pts with mUC. Here, we report preliminary findings from the safety lead-in phase. **Methods:** Eligible pts (≥18 y; ECOG PS ≤1) had mUC, were treatment naive in the advanced/metastatic setting, and unfit for, intolerant to, or refusing platinum-based chemotherapy. Prior anti–PD-1/PD-ligand 1/2 or FGFR inhibitor therapy were not permitted. Pts (regardless of *FGFR* alteration status) were first enrolled in a safety lead-in and received futibatinib 20 mg orally once daily (QD) and pembrolizumab 200 mg IV every 21 d. Dose-limiting toxicities (DLTs) were assessed during the first 21-d treatment cycle. **Results:** As of September 27, 2021, 6 pts were enrolled in the safety lead-in. Median age was 73.5 y (range, 46–84 y) and 17% (1/6) of pts had an ECOG PS of 1. Median duration of treatment was 48 d (range, 21–141 d) with futibatinib and 35 d (1–114 d) with pembrolizumab. Two pts (33%) remained on treatment at data cutoff. Adverse events (AEs) were reported in all 6 pts; AEs in > 2 pts were diarrhea (83%), hyperphosphatemia (67%), increased aspartate aminotransferase (50%), and pruritis (50%). Grade 3 AEs were reported in 2/6 pts: increased aspartate aminotransferase, maculopapular rash, myositis (17% each). There were no grade 4–5 AEs. AEs led to any study drug discontinuation in 3 pts, dose interruption in 3 pts, and dose modification in 3 pts. All 6 pts were evaluated for DLTs after 1 treatment cycle; no DLTs were reported. **Conclusions:** Preliminary safety results support tolerability of futibatinib plus pembrolizumab in platinum-ineligible pts with mUC. As no DLTs were observed in the safety lead-in, the recommended dose of futibatinib in combination with pembrolizumab is 20 mg QD. Enrollment in pts with or without *FGFR* alterations is ongoing to evaluate antitumor activity by *FGFR* alteration status. Clinical trial information: NCT04601857. Research Sponsor: Taiho Oncology, Inc.

502 **Poster Session**

ABLE: Phase 2, single-arm, two-stage study of nabpaclitaxel with anti-PD1/PDL1 in advanced urothelial cancer.

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Background: Anti-PD/PDL1 immune checkpoint inhibitor monotherapy is standard in select PDL1 expressing advanced urothelial cancer (aUC) and platinum-refractory aUC. Nab-paclitaxel (NAB) previously showed encouraging activity in platinum-refractory aUC. We conducted a single-arm trial of the combination of NAB and pembrolizumab in platinum-refractory or cisplatin-ineligible aUC. **Methods:** Eligible patients (pts) had RECIST 1.1 measurable urothelial cancer, grade ≤1 neuropathy, and ECOG PS 0-2. Study therapy consisted of NAB at starting dose of 125 mg/m^2 IV on days 1 and 8 and pembrolizumab 200 mg IV on day 1 in 21-day cycles until progression, intolerable toxicity, death, or consent withdrawal. Continuing NAB after 6 cycles was optional. NAB starting dose was reduced to 100 mg/m^2 after planned interim analysis on the first 17 subjects. Primary endpoint was overall response rate (ORR) by RECIST 1.1. Secondary endpoints included safety/toxicity, progression free survival (PFS), overall survival, complete response proportion, duration of response (DOR), and duration of therapy (DOT). **Results:** Between 2/2018 and 4/2021, 36 response evaluable pts were enrolled; 11 of upper tract origin, 32 men, mean age 71.5 years (range 52 – 88), 25 pure urothelial, 15 platinum-refractory, 21 cisplatin-ineligible by Galsky criteria, and ECOG PS was 0, 1 or 2 in 9, 20, and 7 pts, respectively. Unconfirmed best ORR was 58.3% (95% CI: 42-74) including 3 CR and 18 PR, confirmed ORR 50% (18/36); 31/36 pts experienced some tumor shrinkage. Median DOR was 19 weeks (95% CI: 15.6-34.8), and median PFS 5.4 months (95% CI: 4.6-7.9). Pts received a median of 6 cycles (range 1-14) with median DOT 4.2 months (range 0.6-9.6). Grade ≥3 adverse events (AE) occurred in 25 pts including fatigue (n = 6), anemia (n = 6), peripheral neuropathy (n = 3), and oral mucositis (n = 3); 6 discontinued treatment due to AEs. Ten pts had immune mediated AEs including 1 with encephalitis. Archival tumor NGS revealed TMB ≥10 in 5/21 available. **Conclusions:** The combination of NAB and pembrolizumab exhibited promising activity in advanced urothelial cancer with no unexpected toxicity. Clinical trial information: NCT03240016. Research Sponsor: BMS.

503 **Poster Session**

Phase Ib study of avelumab and taxane based chemotherapy in platinum-refractory or ineligible metastatic urothelial cancer (AVETAX study).

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Background: Metastatic urothelial cancer is aggressive and associated with dismal 5-yr overall survival. Platinum-based chemotherapy and checkpoint inhibitors are standard first-line options with enfortumab vedotin, sacituzumab govitecan, and erdafitinib (in select FGFR altered tumors) subsequently utilized upon disease progression. However, despite these options, long-term outcomes remain poor, and novel strategies are needed to improve oncologic outcomes. We hypothesized that combining avelumab (anti-PD-L1 immunotherapy) with docetaxel is safe and will enhance cancer cell death by releasing neoantigens and potentiating anti-tumor immune-mediated cytotoxicity. **Methods:** This is a phase 1b, single-arm, open-label prospective clinical trial evaluating the combination of avelumab with docetaxel in adult subjects with locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. There are two phases. In Phase 1b, dose de-escalation of docetaxel (Level 0: 75, Level -1: 60 or Level -2: 45 mg/m2) with standard dose avelumab (10 mg/kg) aimed to establish the phase 2 dose in a standard 3+3 design. In dose-expansion, avelumab with the RP2D of docetaxel was evaluated for efficacy. The combination therapy is administered every 3 weeks for 6 cycles, and then avelumab alone is continued every 2 weeks. The primary endpoint is safety. Efficacy endpoints include objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). **Results:** At the cutoff date of 10/8/2021, 21 patients were enrolled in the study. Only one of the 6 patients treated with level 0 dose of docetaxel had dose-limiting toxicity (neutropenic fever). Docetaxel at 75 mg/m2 along the avelumab was deemed safe for dose expansion cohort. An additional 15 patients were enrolled in the dose-expansion cohort. Of the 20 evaluable patients, ORR (CR+PR) was seen in 70% of subjects. (CR: 30%, PR: 40%, SD: 5%, PD: 25%, and 1 patient was not evaluable). The median PFS was 9.2 months (range: 1.5 – 25.8 months), and median OS was not reached. The most common Grade 3 or 4 AEs were febrile neutropenia, transaminitis, diarrhea, anemia, and neutropenia. No treatment-related deaths were noted. **Conclusions:** The combination of avelumab with docetaxel is safe with promising efficacy that is worth further studying in patients with platinum-refractory or ineligible metastatic urothelial cancer. Clinical trial information: NCT03575013. Research Sponsor: Grant from Holden Comprehensive Cancer Center, Pharmaceutical/Biotech Company.

504 **Poster Session**

A multicenter real-life U.K. study of use of immunotherapeutic agents in metastatic urothelial cancer.

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Background: First-line chemotherapy for patients with cisplatin-ineligible metastatic urothelial carcinoma (mUC) is associated with short response duration and high toxicity. Pembrolizumab(PEM) and atezolizumab (ATZ) are associated with long-term, durable remissions as a first-line treatment of cisplatin-ineligible, PD-L1-positive patients with mUC. For patients who progressed during or after platinum-based chemotherapy, Immunotherapy also prolongs survival with less toxicity and better quality of life compared with further lines of chemotherapy. There have been no studies directly comparing the effectiveness of PEM to ATZ in mUC patients. **Methods:** A cohort of 112 patients from 3 UK centres were included. 62, previously untreated cisplatin ineligible mUC patients who showed PDL1 positivity were given either ATZ or PEM once every 3 weeks until progression. 49 patients who had initial platinum based chemotherapy subsequently had ATZ or PEM as second line treatment following their disease progression The primary endpoint was Overall Survival(OS) and secondary endpoints included objective rate(ORR), response duration and safety. **Results:** The median age was 69 (Interquartile range 43-91) and 23% were female and 77% were male. Among, patients who received immunotherapy 1st line, 82% had baseline renal impairment(GFR $<$ 60), and 18% had Eastern Cooperative Oncology Group performance status 2. For chemo naïve patients, median OS was 11.5 months for PEM and 5 months for ATZ respectively. ORR was 22 % for ATZ vs 50% for PEM and median duration of treatment was 4.5 and 2.5 months for PEM and ATZ respectively. When used in 2nd line median OS is 7 months for ATZ irrespective of PDL1 status and not reached for PEM yet. Grade 2 and above toxicities were reported in 18 % ATZ patients vs 10% in PEM patients, commonest were pneumonitis, tiredness, hepatitis and dermatitis. No treatment related deaths were reported. **Conclusions:** This study suggests that pembrolizumab has higher response rate and better survival compared to atezolizumab in cisplatin-ineligible patients with mUC and also in the 2nd line setting after disease progression following platinum based agents. Both agents were well tolerated. Research Sponsor: None.

505 **Poster Session**

Association of time to second-line (2L) immune-checkpoint inhibitors (ICI) and outcomes with ICIs in patients (pts) with advanced urothelial carcinoma (aUC).

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Background: Current standard therapy for most pts with aUC is first-line (1L) platinum-based chemotherapy followed by ICI maintenance (or 2L if progression). Shorter time on 1L or between therapy lines may be a surrogate of more aggressive disease and poor outcome, but its prognostic role in ICI response is unclear. We hypothesized that shorter time until start of 2L ICI would be associated with worse outcomes in aUC. **Methods:** We performed a retrospective multi-institution cohort study in pts with aUC treated with 1L platinum-based chemotherapy, who later received 2L ICI. Pts receiving maintenance ICI were excluded. We calculated the time from start of 1L platinum chemotherapy to start of 2L ICI, dichotomizing the exposure into ≤6 months and >6 months. We compared overall response rate (ORR) to 2L ICI, progression-free survival (PFS) and overall survival (OS) from the start of 2L ICI between the two populations. ORR was compared among groups using multivariable logistic regression and PFS, OS using cox regression. Analysis was adjusted for calculated Bellmunt score. **Results:** From a total of 1283 pts, 462 received 1L platinum chemotherapy; among those, 350 received 2L ICI. After exclusions, 270, 269 and 260 pts were included in the ORR, PFS and OS analyses, respectively. Median age was 70 years, 78% men, 75% White, 74% with pure urothelial histology, 21% upper tract, 60% received cisplatin in 1L. Pts with time to 2L ICI ≤6 months had significantly higher Bellmunt scores (32% vs 22% score=2, 9% vs 3% score=3). ORR and PFS were comparable between pts with ≤ and >6 months to 2L ICI. However, OS was significantly longer for pts with >6 months to 2L ICI (median [m]OS 13 vs 7 months, p=0.002), (Table). **Conclusions:** Among pts with aUC treated with 2L ICI, time to 2L ICI ≤6 months from 1L platinum based chemotherapy was associated with similar ORR and PFS but shorter OS. Limitations include retrospective nature, patient selection, confounding factors. More studies are needed on the impact of platinum resistance in pts with aUC treated with ICIs. Research Sponsor: None.

Time to 2L ICI	ORR (95% CI)	aOR (95% CI)	mPFS (months, 95% CI)	aHR (95% CI)	mOS (months, 95% CI)	aHR (95%CI)
≤6 mo	25 (18-33)	(ref)	4 (3-4)	(ref)	7 (5-9)	(ref)
>6 mo	25 (18-33)	1.04 (0.56-1.95)	4 (4-6)	0.78 (0.58-1.05)	13 (9-16)	**0.60*** (0.43-0.82)

506 **Poster Session**

NEXT: A single-arm, phase 2, open-label study of adjuvant nivolumab after completion of chemo-radiation therapy in patients with localized muscle-invasive bladder cancer.

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Background: Nivolumab has known efficacy as adjuvant therapy after radical cystectomy in localized muscle invasive bladder cancer (MIBC). We are evaluating the efficacy of nivolumab adjuvant to definitive chemo-radiation therapy (CRT) in MIBC. **Methods:** In the NEXT study, we are currently enrolling patients with localized MIBC undergoing standard CRT. Participants are started on nivolumab 480 mg IV every 4 weeks (up to 12 doses) within 90 days of completion of CRT. Cystoscopic and scan-based assessments are done every 3 months for the first two years (yrs). The primary endpoint is failure-free survival (FFS) at 2 yrs from the start of CRT, with failure defined as local or systemic disease recurrence. Secondary endpoints include toxicity and quality of life (QOL) assessments. We have planned correlative studies on peripheral blood and tumor tissue. We performed a protocol-defined interim safety and efficacy analysis to assess the 6-month FFS rate with CRT and adjuvant nivolumab. **Results:** From 8/03/2017 to 9/28/2021, 20 patients were enrolled at two centers; median age is 76 yrs, clinical stage range is T2-T4b, N0-N+, M0; the median number of nivolumab cycles is 6.5, and the median follow-up is 8.9 months. The estimated 6-month FFS rate is 88.2% (95% CI 74.2% - 100%). Disease has progressed in 9 patients, of which 4 have local bladder recurrence (T1 in 3/4) and 5 have distant metastases. The estimated median FFS is 17.1 months (95% CI 8.71 months - infinity). Grade ≥3 treatment-related adverse events (AEs) are noted in 3/20 patients (15%): elevated transaminases, diarrhea, and polymyalgia rheumatica. Grade 3 radiation therapy oncology group (RTOG) AEs occurred in 2 patients. QOL measures are serially evaluable in 13 patients for the first 3 months of adjuvant nivolumab, and are stable in the domains of disease-related physical symptoms, treatment side effects, and function/well-being, while are significantly improved (p=0.023) in the domain of disease-related emotional symptoms. **Conclusions:** In this first report of the role of immunotherapy adjuvant to CRT for localized bladder cancer, adjuvant nivolumab is well tolerated and has promising efficacy. Clinical trial information: NCT03171025. Research Sponsor: Bristol Myers Squibb.

507 **Poster Session**

Favorable toxicity of chemoradiation for muscle-invasive bladder cancer in elderly, frail patients.

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Background: Chemoradiation (CRT) for bladder cancer provides comparable outcomes to radical cystectomy; however, concerns regarding toxicity, particularly in elderly, frail patients limit its utilization. **Methods:** We identified 150 consecutive patients who underwent definitive CRT for T1-4N0M0 bladder cancer at Memorial Sloan Kettering Cancer Center between 2005 and 2020. Most were men (71.3%), elderly (median age, 77.5 years), had high Charlson Comorbidity Index (CCMI) score (median, 7), were nonsurgical candidates (65.3%), Stage T2 (75.3%) and had a macroscopically complete TURBT (65%). 24% of patients received neoadjuvant platinum-based chemotherapy. Concurrent gemcitabine was used in 98.7%. 116 (77.3%) patients underwent 45Gy to the pelvic lymphatics/whole bladder followed by bladder boost (median total dose, 66.6 Gy) and 34 patients (22.7%) received 55 Gy in 20 fractions to the whole bladder/ urethra only. Fiducial markers for image-guidance were used in 55% (83/150) of cases. Patients were followed post-treatment with toxicity assessment, cytology/cystoscopy and imaging every 3 months year 1, every 6 months for years 2-3 and annually thereafter. Acute ($\leq$3 months) and late ($>$ = 3 months) gastrointestinal (GI) and genitourinary (GU) toxicities were assessed according to CTCAE v4.0. Complete response (CR) was defined as no evidence of disease at 3-month follow up. Survival outcomes were estimated using the Kaplan-Meier method. Median follow up was 31 months (range, 0-155 months). **Results:** The majority (94%) completed the prescribed course of radiation. Acute grade 3 GU and GI toxicities occurred in 2% and 5.3% of patients, respectively. No acute grade 4 toxicity was recorded. The most common GU and GI toxicities were radiation cystitis and diarrhea. Late grade $\geq$2 GU and GI toxicity occurred in 11.2% and 0.7% or cases, respectively. One late grade 4 GI toxicity was recorded (small bowel obstruction 7 months after completion of CRT). 80% (n = 120) of patients achieved a CR. Of complete responders, 30% (36/120) developed recurrent disease at a median time of 13.8 months (range, 3.2- 90.4). Among them, local only vs regional/distant recurrence rates were 72.2% and 27.8%, respectively. Of entire cohort, 40% of patients were alive and 31% had died with no evidence of disease at last follow up. While the estimated 5-year OS was 48% (95% CI, 39%, 59%), the estimated 5-year disease-specific mortality rate was 31% (95% CI, 24%, 40%). On univariate analysis, younger age ($p < 0.001$), receipt of neoadjuvant chemotherapy ($p = 0.006$) and surgical candidacy ($p = 0.041$) were predictive of improved OS. On multivariate analysis, only younger age was significant ($p = 0.006$). **Conclusions:** CRT had a favorable toxicity profile and encouraging cancer control outcomes in this unselected, mostly elderly and frail patient cohort. Research Sponsor: None.

508 **Poster Session**

Recombinant humanized Anti-PD-1 monoclonal antibody toripalimab in patients with metastatic urothelial carcinoma (POLARIS-03 study): Two-year survival update and biomarker analysis.

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Background: Patients with advanced metastatic urothelial carcinoma (mUC) who experience disease progression after standard therapy have limited treatment options. Toripalimab was approved for the 2nd line treatment of mUC based on a phase II clinical study (POLARIS-03) in Chinese patients with mUC (Clinical trial ID: NCT03113266). Here we report the two-year OS update and biomarker analysis of the study. **Methods:** Metastatic UC Patients received toripalimab 3 mg/kg Q2W until disease progression, unacceptable toxicity or voluntary withdrawal. Clinical response was assessed every 8 weeks. Tumor PD-L1 expression, tumor mutational burden (TMB), and other biomarkers were evaluated for correlation with clinical response. **Results:** From May 2017 to September 2019, 204 patients were screened and 151 patients were enrolled from 15 participating centers. By cutoff date of September 8, 2021, no emergent of new safety signal was identified compared with the previous one-year report. By the cutoff date, 91 patients have died, and the median OS was 14.6 months. Whole exome sequencing (WES) was performed on tumor biopsies and paired PBMCs and the results were available from 135 patients. Patients with mutations in chromatin remodelers SMARCA4/PBRM1 or tumor suppressor RB1 were associated with better responses to toripalimab than patients with wild-type genes. The ORR was 30% (6/20) in patients with FGFR2/FGFR3 mutations or FGFR2/FGFR3 gene fusions, and 42% (5/12) in patients with NECTIN4 genomic alternations. The median TMB value was 4.1 mutations per million base pairs (Mb) in the cohort. Using 10 mutations/Mb as the cut off, TMB-high patients (n = 27) had better ORR than TMB low patients(n = 108) (48% versus 22%, p = 0.014). The TMB-high group also showed better PFS (12.9 versus 1.8 months, HR = 0.48 [95% CI:0.31-0.74], $p < 0.001$) and OS (not reached versus 10.0 months, HR = 0.53 [95% CI:0.32-0.88], p = 0.013) than the TMB low group. **Conclusions:** Toripalimab has demonstrated a manageable safety profile and encouraging clinical activity in metastatic UC patients refractory to 1st line chemotherapy. WES analysis identified divergent mutations in the study. We report the utility of TMB to predict not only the response rate but also the PFS and OS benefits in patients with mUC in response to an ICI monotherapy. Clinical trial information: NCT03113266. Research Sponsor: Shanghai Junshi Bioscience Co., LTD, Shanghai, China.

509 **Poster Session**

Safety and efficacy of neoadjuvant intravesical oncolytic MV-NIS in patients with urothelial carcinoma.

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Background: Bladder cancer is a leading cause of cancer death in the United States. The histology in $>$ 90% of cases is urothelial carcinoma (UC). Tumors may present either as non-muscle-invasive (NMIBC) or muscle-invasive disease (MIBC). Current standard of care for patients with high risk NMIBC includes transurethral resection of bladder tumor (TURBT) followed by intravesical immunotherapy with Bacillus Calmette-Guerin (BCG). Meanwhile, patients with BCG unresponsive NMIBC or MIBC are recommended to undergo radical cystectomy (RC), which adversely impacts quality of life and is associated with significant morbidity. MV-NIS is an investigational oncolytic measles virus with an excellent clinical safety profile. This ongoing phase I clinical study is designed to test the safety, efficacy and identify the recommended phase 2 dose (RP2D) of intravesical MV-NIS in patients with NMIBC or MIBC who are scheduled for RC and not eligible for neoadjuvant chemotherapy. **Methods:** Bladder UC patients were evaluated for eligibility and provided informed consent prior to enrolling. To date 8 patients have been enrolled: 4 to the single dose safety cohort, and 4 to the multi-dose expansion cohort. Patients were administered intravesical ~$1x10^9$ $TCID_{50}$ MV-NIS once at least 1 week prior to RC (safety cohort), or twice at 4 and 2 weeks prior to RC (expansion cohort). Patients were closely monitored during the 2-hour instillation period. Tumor specimens from the pre-treatment TURBT and post-treatment RC were analyzed to determine pre- and post-treatment pathological stage and evaluate tumor killing and immune cell infiltrate. **Results:** Intravesical MV-NIS treatment was well tolerated in all patients. Only a single Adverse Event (AE) attributable to MV-NIS treatment (Grade 1 hematuria). AEs Grade $>$ 2 were related to post-surgical complications. Tumor downstaging was observed in 4 of 8 patients. Among 4 patients in the expansion cohort, 2 had no residual disease (pT0). Central assessment of RC tissues showed significant inflammatory infiltrate in all treated bladder specimens. Detailed analyses are ongoing to characterize MV infection and immune infiltrate in bladder tissue. **Conclusions:** The higher-than-expected rate of tumor downstaging and pT0 pathology, paired with the significant immune infiltrate observed in post-treatment bladder tissue, provide compelling evidence that intravesical MV-NIS has clinical activity against UC. These results support the use of two doses of ~$1x10^9$ $TCID_{50}$ as the RP2D in future clinical studies for BCG unresponsive NMIBC or MIBC patients. MV-NIS induced inflammation may act synergistically with checkpoint blockade therapies. Clinical trial information: NCT03171493. Research Sponsor: U.S. National Institutes of Health., Pharmaceutical/Biotech Company.

510 **Poster Session**

Interim results of a phase Ib single-center study of pembrolizumab in combination with chemotherapy in patients with locally advanced or metastatic small cell/neuroendocrine cancers of the prostate and urothelium.

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Background: Small cell/neuroendocrine cancers irrespective of origin share aggressive phenotypes. Pembrolizumab (MK-3475) is a humanized antibody targeting programmed cell death protein 1 (PD-1) that has shown activity against small cell lung cancers. Preclinical studies showed molecular commonality amongst small cell/neuroendocrine cancers across multiple tissue types. This study evaluated the safety and efficacy signals of pembrolizumab and chemotherapy in patients with small cell/neuroendocrine cancer of the prostate and urothelium. **Methods:** Patients with locally advanced or metastatic small cell cancer of the bladder or upper urinary tract (cohort 1) and primary small cell or treatment-derived neuroendocrine prostate cancer (NEPC) (cohort 2) received pembrolizumab and standard of care chemotherapy (etoposide and cisplatin/carboplatin for cohorts 1 and 2, with option of docetaxel and carboplatin for cohort 2) with maintenance pembrolizumab for 2 years until unequivocal progressive disease or unacceptable toxicity. The primary endpoint was to estimate ORR and PFS compared to historical controls as well as safety and tolerability. Pretreatment targeted gene mutation sequencing was performed. **Results:** 14 patients were enrolled (7 cohort 1, 7 cohort 2) with mean age 64.9 (range 53 to 81). ORR across cohorts was 43% (95% CI: (0.17, 0.69)), and 43% (95% CI: (0.06, 0.80)) within each cohort. PFS rate at 12 months (proportion of patients who have not progressed at 12 month) was 61% (95% CI: (0.40,0.95)) across cohorts, 86% (95% CI: (0.63,1.00)) within cohort 1, and 36% (95% CI: (0.12,1.00)) within cohort 2. 3 patients in cohort 1 with locally advanced disease exhibited SD and underwent radical cystectomy, with one patient pT0 and no PD at a mean follow up of 20 months. Grade 3 or higher AEs occurred in 71% of patients, while 29% of patients experienced grade 3 or higher AEs related to pembrolizumab. No patients died or discontinued therapy secondary to adverse treatment effects. In 12 patients where tissue was sufficient, all patients had genomic alterations in either *p53* (75%) or *Rb* (58%). Of the 5 available patients with NEPC, 60% had alternations in DNA damage response genes. **Conclusions:** In patients with locally advanced or metastatic small cell/neuroendocrine prostate and bladder cancers, combination pembrolizumab with standard of care chemotherapy and maintenance pembrolizumab showed promising efficacy with tolerable adverse events. Clinical trial information: NCT03582475. Research Sponsor: Merck Sharp & Dohme Corp.

511 **Poster Session**

Phase 2 trial of CV301 vaccine plus atezolizumab (Atezo) in advanced urothelial carcinoma (aUC).

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Background: PD(L)1 inhibitors can achieve durable responses in aUC but only in a minority of patients (pts). Combination strategies with agents that "prime and stimulate" the immune system may improve outcomes. CV301 comprises 2 recombinant poxviruses, Modified Vaccinia Ankara (MVA) and Fowlpox (FPV), encoding the human transgenes for CEA, MUC-1, and a Triad of Co-stimulatory Molecules (TRICOM: ICAM-1, LFA-3, and B7-1). MVA-CV301 is used for priming and FPV-CV301 is used for booster doses. Preliminarily, BN-platform vaccine plus PD-(L)1 inhibitors exhibited synergistic preclinical anti-tumor efficacy and the combination of CV301 and anti-PD-(L)1 agent demonstrated an acceptable safety profile. We hypothesized that this combination would be safe and effective in cisplatin-ineligible or platinum-refractory pts with aUC. **Methods:** A Phase 2, single-arm multicenter trial was designed to study CV301 + atezo as 1st-line treatment in pts with aUC ineligible for cisplatin-based chemotherapy regardless of PD-L1 status (Cohort 1; C1) and in pts progressing on/after platinum-based chemotherapy (Cohort 2; C2). MVA-CV301 was given subcutaneously (SC) on Days 1 and 22 and FPV-CV301 SC from day 43 every 21 days for 4 doses, then every 6 weeks until 6 months, then every 12 weeks until 2 years. Atezo 1200mg IV was given every 21 days. Primary endpoint: objective response rate (ORR). Secondary endpoints: OS, PFS, response duration, AEs and antigen-specific T-cell responses to CEA and MUC-1 by ELISPOT. Using 1-sided α 2.5%/cohort, a 2-stage design with 14/19 and 13/22 stage 1/2 subjects, respectively, will achieve $\geq$70% power if the true ORR for C1 is 43% and C2 is 33%. 3 C1 and 2 C2 responders were required in stage 1 to move forward. **Results:** 43 evaluable pts were enrolled and received therapy: 19 in C1; 24 in C 2. Overall, 9 pts experienced $\geq$ Grade 3 AEs related to the combination of treatment: 5 in C1, and 4 in C2. In C1, 1 pt had partial response (PR), for ORR 5.3% (90%CI: 0.3, 22.6) and 5 (26.3%, 90%CI: 11.0, 47.6) had stable disease (SD) as best response. In C2, 1pt had CR and 1 had PR, for ORR 8.3% (90%CI: 1.5, 24.0) and 3 (12.5%, 90%CI: 3.5, 29.2) had SD as best response. Median PFS and OS in C1 were 2.0 mo and 13.8 mo, and in C2 1.95 and 8.13 mo, respectively. The trial was halted for futility. Responding pts in C2 exhibited T-cell responses to CEA and pts with SD exhibited responses to MUC-1. **Conclusions:** CV301 + atezo exhibited an acceptable safety profile but did not demonstrate sufficient efficacy in pts with aUC as 1st-line therapy in cisplatin-ineligible pts or in the platinum-refractory setting. The development of effective vaccines to generate robust and durable responses as single agents and/or combined with anti-PD(L)1 remains an unmet need in aUC. Clinical trial information: NCT03628716. Research Sponsor: Bavarian Nordic.

Post hoc analysis of the efficacy of pembrolizumab retreatment after progression of advanced urothelial carcinoma (UC) in KEYNOTE-045 and KEYNOTE-052.

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Background: Pembrolizumab (pembro) has shown efficacy in advanced/unresectable and metastatic UC (mUC). There is interest in determining whether pts should be treated subsequently with checkpoint inhibitors such as anti–PD-1 therapy if mUC responds then later progresses. Pembro retreatment after disease progression has shown efficacy in melanoma and NSCLC. This post hoc exploratory analysis investigated the efficacy of pembro retreatment for pts with advanced UC or mUC enrolled in KEYNOTE-045 and KEYNOTE-052 with a best overall response (BOR) of SD or better and whose disease progressed after discontinuation or completion of 2 y of therapy. **Methods:** The phase 3 KEYNOTE-045 trial (NCT02256436) was designed to compare the efficacy and safety of pembro vs chemotherapy (chemo) in pts with mUC that recurred/progressed on platinum containing chemo; ≤2 prior lines of systemic chemo for mUC were permitted. The phase 2 KEYNOTE-052 trial (NCT02335424) was designed to evaluate the efficacy and safety of first-line pembro in cisplatin-ineligible pts with advanced UC. In both studies, pembro was administered for up to 2 y; pts were eligible for retreatment if they stopped pembro after CR or had a BOR of CR, PR, or SD and completed 2 y of treatment. Pts must have investigator-confirmed radiographic PD after therapy cessation, have ECOG PS score 0-1, and not have received anticancer treatment after the last pembro dose. BOR to retreatment is reported. **Results:** At data cutoff for KEYNOTE-045 (Oct 1, 2020), 11 pts were retreated: 5 (45%) achieved objective response to retreatment (3 CR; 2 PR; Table) and 6 had SD, for a disease control rate (DCR; CR+PR+SD) of 100%. Median treatment-free interval was 7.7 mo (IQR, 3.6-16.5); median duration of retreatment was 11.4 mo (IQR, 7.6-12.0). Seven pts (64%) were alive at cutoff. At data cutoff for KEYNOTE-052 (Sep 26, 2020), 10 pts were retreated; 5 (50%) had objective response to retreatment (1 CR; 4 PR) and 4 had SD, for a DCR of 90%. Retreatment BOR was PD for 1 pt (10%). Median treatment-free interval was 13.0 mo (9.2-16.6); median duration of retreatment was 6.0 mo (IQR, 4.9-9.2). Four pts (40%) were alive at cutoff. **Conclusions:** Although the number of pts who received retreatment was small, objective responses were observed. The findings are generally consistent with observations from retreatment in other tumor types (e.g., melanoma). Clinical trial information: NCT02256436 and NCT02335424. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

BOR to Retreatment by First BOR, n (%)				
First BOR	KEYNOTE-045 RetreatmentCR	KEYNOTE-045 RetreatmentPR	KEYNOTE-045 RetreatmentSD	KEYNOTE-045 RetreatmentPD
CR (n = 5)	3 (27)	1 (9)	1 (9)	0 (0)
PR (n = 5)	0 (0)	1 (9)	4 (36)	0 (0)
SD (n = 1)	0 (0)	0 (0)	1 (9)	0 (0)
First BOR	KEYNOTE-052 RetreatmentCR	KEYNOTE-052 RetreatmentPR	KEYNOTE-052 RetreatmentSD	KEYNOTE-052 RetreatmentPD
CR (n = 6)	1 (10)	3 (30)	2 (20)	0 (0)
PR (n = 4)	0 (0)	1 (10)	2 (20)	1 (10)

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Targeting urothelial neoplasia using an investigational virus-like drug conjugate.

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Background: Human papillomavirus virus-like particles (HPV VLP) preferentially target tumor cells via cell surface modified heparan-sulfate proteoglycans (HSPG). The investigational virus-like drug conjugate, belzupacap sarotalocan (AU-011), is currently in phase 2 clinical trials for treatment of primary choroidal melanoma. We previously demonstrated AU-011's *in vivo* tumor acute cytotoxicity upon activation with near-infrared light (nIR), resulting in tumor-free survival for at least 100 days and protection from tumor re-challenge in the MB49 murine flank model of bladder cancer. Here we provide additional data supporting further clinical development in urothelial neoplasia as an additional oncology indication. **Methods:** We examined the cytotoxicity of AU-011 in a panel of six human bladder cancer cell lines *in vitro* and binding and distribution in human tumor biopsy samples *ex vivo*. Tumor distribution of AU-011 was also assessed *in vivo* after intravesical instillation in the orthotopic MB49 murine model. In consideration of the glycocalyx layer often found coating the interior of the bladder wall and the surface of bladder tumors, pre-treatment with hyauronidase was tested both on human biopsy samples and in the murine orthotopic model. Lastly, tumor distribution of AU-011 was evaluated when formulated with the polyamide Syn3. **Results:** When tested *in vitro* on a panel of human bladder tumor cell lines representing grades I-IV carcinomas, we found AU-011's potency to be in the picomolar range (EC50 range 16.6 pM – 62.75 pM). We assessed the VLPs ability to bind *ex vivo* to a panel of human urothelial tumor biopsies and observed binding in samples representing both invasive T2 and non-invasive Ta papillary tumors. Tumor biopsy samples were pre-treated with hyaluronidase to break down the glycocalyx layer surrounding the tumor, and an increase in signal was observed in the Ta biopsy sample. Similarly, using the orthotopic MB49 murine tumor model with intravesical delivery of AU-011, we observed an enhancement of AU-011 distribution into the tumor when the bladders were pre-treated with hyaluronidase. Additionally, when formulated with Syn3, AU-011 distribution throughout the tumors was augmented without the need for hyaluronidase pre-treatment. **Conclusions:** We have demonstrated AU-011 targeted cytotoxicity *in vitro* using a panel of human bladder cancer cell lines indicating that its binding to bladder cancer cells is tumor grade and genetic mutation agnostic. Additionally, tumor binding and distribution was observed *ex vivo* using human bladder cancer biopsy samples and *in vivo* in the murine MB49 orthotopic model. Human and murine tumor distribution was improved with a pre-treatment of hyaluronidase or when formulated with Syn3. Collectively, these data support the further investigation of the use of AU-011 for the indication of uroepithelial cancer. Research Sponsor: Aura Biosciences., U.S. National Institutes of Health.

515 **Poster Session**

Study RC48-C014: Preliminary results of RC48-ADC combined with toripalimab in patients with locally advanced or metastatic urothelial carcinoma.

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Background: RC48-ADC is a novel humanized anti-HER2 antibody-drug conjugate (ADC), which showed promising data in HER2-positive and even negative patients (pts) with metastatic urothelial carcinoma (mUC). Toripalimab is an anti-PD-1 antibody with a durable antitumor effect for mUC. The combination may have a synergistic antitumor effect. Initial RC48-C014 data was previously presented (ASCO 2021); here we reported an update on safety and ORR. **Methods:** In dose-escalation cohort, pts received 1.5 or 2 mg/kg RC48-ADC + 3mg/kg toripalimab with the traditional 3+3 escalation design. In the expansion cohort, patients received the recommended dose of RC48-ADC + toripalimab every 2 weeks. The primary endpoints were safety/tolerability and recommended RC48-ADC dose; secondary endpoints included pharmacokinetics, ORR per RECIST 1.1, PFS, and OS, stratified by HER2 and PD-L1 expression. **Results:** As of 23 Sep 2021 (data cutoff), 32 mUC pts (18 males; median age 67 y [52-76]) were enrolled since 20 Aug 2020. Fifty-three percent pts were systemic treatment naïve in the locally advanced or metastatic setting. The primary site was in upper tract UC in 56%; 53% had visceral metastases (mets), including 28% with liver mets; HER2 expression was positive (IHC 3+ or 2+ ISH+) in 19% pts, and PD-L1 CPS$\geq$1 in 56%. No dose-limiting toxicity was reported, and the recommended dose for RC48-ADC was 2mg/kg. At data cutoff, confirmed investigator-assessed ORR was 75% (95%CI: 50.9, 91.3), including 15% CRs; DCR was 95% (95%CI: 75.1, 99.9). The ORR for 1L previously untreated mUC pts was 80% and 75% for pts with liver mets. The ORR was 100% for pts with HER2 (3+), 77.8% for HER2 (2+), 66.7% for HER2 (1+), and 50% for HER2 (0) respectively. The ORR was 97.1% in pts with PD-L1 CPS$\geq$1 and 50% in CPS $<$ 1. Follow-up continues for PFS and OS. Most common treatment-related AEs were anorexia (72%), asthenia (56%, 8%$\geq$G3), aminotransferase level increased (56%, 4%$\geq$G3), peripheral sensory neuropathy (56%), alopecia (52%), nausea (36%), and anemia (32%). The most common immune-related AE was pneumonitis (20%). **Conclusions:** RC48-ADC in combination with toripalimab demonstrated promising efficacy in pts with mUC and a manageable safety profile. Further evaluation of RC48 + toripalimab in mUC is ongoing. Clinical trial information: NCT04264936. Research Sponsor: Remegen.

Impact of primary tumor location on efficacy and safety of pembrolizumab (pembro) in patients (pts) with locally advanced or metastatic urothelial carcinoma (UC) enrolled in the phase 2 KEYNOTE-052 and phase 3 KEYNOTE-045 trials.

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Background: Pembro showed antitumor activity in 1L and 2L for pts with UC in the single-arm, phase 2 KEYNOTE-052 study (NCT02335424) and the randomized phase 3 KEYNOTE-045 (NCT02256436) study, respectively. This post hoc exploratory analysis evaluated whether primary tumor location affected efficacy and safety of pembro (KEYNOTE-052; KEYNOTE-045) and chemotherapy (chemo; KEYNOTE-045). **Methods:** KEYNOTE-052 enrolled cisplatin-ineligible pts with advanced/metastatic UC who had not previously received systemic therapy; they received pembro (200 mg IV Q3W). KEYNOTE-045 enrolled pts with advanced/metastatic UC who had received platinum-containing chemo; pts were randomly assigned 1:1 to receive pembro (200 mg IV Q3W) or investigator's choice of chemo (paclitaxel, docetaxel, or vinflunine). Both studies required pts to have measurable disease per RECIST v1.1. Upper tract (UT) UC included primary tumors in the renal pelvis or ureter; lower tract (LT) UC included primary tumors in the bladder or urethra. Pts with UT and LT disease (UT/LT) were classified as LT. Pts receiving pembro were treated until disease progression, unacceptable toxicity, or withdrawal of consent, for up to 2y. End points were PFS, ORR, and DOR per RECIST v1.1 by central radiology assessment and OS. **Results:** A total of 369 pembro-treated pts (68 UT; 301 LT [79 UT/LT]) from KEYNOTE-052 plus 270 pembro-treated pts (93 UT; 177 LT [33 UT/LT]) and 272 chemo-treated pts (94 UT; 178 LT) from KEYNOTE-045 were evaluated. Median follow-up from randomization to data cutoff (09/26/20 and 10/1/20, respectively) was ≥56 mo. Both studies enrolled a similar percentage of pts with PD-L1–positive tumors (25%-30%). PFS, ORR, DOR, and OS for pembro were consistent regardless of tumor location, although ORR for KEYNOTE-045 was lower for the UT group (Table). In the chemo arm of KEYNOTE-045, similar efficacy was observed regardless of tumor location or regimen. Grade 3-5 TRAEs occurred at similar rates in KEYNOTE-052 (19.1% UT; 21.6% LT) and KEYNOTE-045 (17.2% UT; 16.8% LT). **Conclusions:** In this exploratory analysis, pembro showed similar clinical activity and manageable safety regardless of primary UC tumor location. Clinical trial information: NCT02256436 and NCT02335424. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Efficacy results by study and tumor location in pembro-treated patients.

	KEYNOTE-052 Upper (n = 68)	KEYNOTE-052 Lower (n = 301)	KEYNOTE-045 Upper (n = 93)	KEYNOTE-045 Lower (n = 177)
ORR, % (95% CI)	26.5 (16.5-38.6)	29.6 (24.5-35.1)	14.0 (7.7-22.7)	26.0 (19.7-33.1)
DOR, median (range), mo[a]	35.8 (2.8 to 57.3+)	33.2 (1.4+ to 60.7+)	24.6 (6.2+ to 51.1+)	29.7 (1.6+ to 60.5+)
OS, median (95% CI), mo	10.8 (7.6-17.0)	11.5 (9.7-13.1)	9.7 (7.7-14.0)	10.1 (7.3-12.5)
PFS, median (95% CI), mo	2.8 (1.9-3.5)	2.5 (2.1-3.4)	2.1 (2.0-2.2)	2.1 (2.0-3.4)

[a]+ indicates no progressive disease by the time of last disease assessment.

517 **Poster Session**

Safety lead-in of phase II SBRT and durvalumab with or without tremelimumab for unresectable and cisplatin-ineligible, locally advanced or metastatic bladder cancer.

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Background: Many patients with muscle-invasive bladder cancer are not ideal candidates for chemotherapy or radical cystectomy. Moreover, local progression may further impair quality of life. Bladder preservation with maximal transurethral resection of bladder tumor (TURBT) and stereotactic body radiotherapy (SBRT) is a viable treatment option for such patients, offering durable local control while potentiating the effect of immunotherapy. Herein, we report on the safety profile of SBRT in combination with durvalumab (anti-PDL1) and tremelimumab (anti-CTLA4) in the safety lead-in cohort of an institutional Phase II trial for cisplatin-ineligible, unresectable locally advanced or metastatic bladder cancer patients. **Methods:** Patients with locally advanced or metastatic urothelial carcinoma, who were unwilling or unable to undergo radical cystectomy and/or systemic chemotherapy were eligible. Patients received maximal TURBT, followed by durvalumab 1500mg IV every 4 weeks and bladder SBRT 33Gy in 5 fractions between the first 2 cycles. After 6 such patients did not experience a dose limiting toxicity, tremelimumab 75mg IV was added for cycles 1-2. Patients were followed with CT Chest/Abdomen/Pelvis and cystoscopy every 3 months. Treatment-related adverse events (TRAEs) were assessed per CTCAE 5.0 and progression was assessed per RECIST 1.1. **Results:** Between January 2019 and May 2020, 10 patients received TURBT followed by SBRT and durvalumab (Age 73-96, 3 Female, 7 ECOG 1, 3 ECOG 0). Five patients had localized disease and 5 had nodal or distant metastases. Median cycles of durvalumab was 12.5 (2-13), and 4 patients received 2 cycles of tremelimumab. At a median follow-up of 16.8mo (6.4-30mo), there were 2 Grade 3+ immunotherapy-related TRAEs (1 Grade 3 lipase elevation self-resolved, 2 Grade 3 myositis treated with steroids). The most common TRAEs of any grade included pancreatic enzyme elevation (3 patients), rash (3 patients), and urinary symptoms related to RT (3 patients). Disease control rate 70% and local control was 90%. There were 3 non-treatment related deaths. **Conclusions:** Bladder SBRT with durvalumab and tremelimumab was well tolerated and demonstrated promising local control in the safety lead-in cohort. Clinical trial information: NCT03601455. Research Sponsor: AstraZeneca.

A systematic review and network meta-analysis evaluating neoadjuvant treatments in muscle-invasive bladder cancer.

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Background: Cisplatin (C) based neoadjuvant chemotherapy (NAC) has been the mainstay treatment for muscle invasive bladder cancer (MIBC). However, the optimal choice of NAC is not well-established. We therefore conducted a network-meta-analysis (NMA) to assess comparative efficacy of different treatment options. **Methods:** Several electronic databases (MEDLINE, and EMBASE) and conference proceedings were systematically used to identify randomized trials evaluating first-line treatments in neoadjuvant MIBC. Outcomes of interest included overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and pathologic complete response (pCR). DerSimonian-Laird random-effects meta-analysis was used to compute direct comparisons between NAC and local therapy (LT) only. Fixed effect NMA was conducted within the frequentist framework for mixed treatment comparisons. P-scores were used to assess relative treatment rankings. All statistical analyses were conducted in R (v 4.1.1). **Results:** This systematic review included 23 trials (25 references) with a total of 5313 patients with 10 unique treatments. Direct comparisons showed significant benefit in PFS (HR: 0.82; 95% CI: 0.71-0.94), and in OS (HR: 0.85; 95% CI: 0.78-0.92) with NAC when compared to LT only. However, the likelihood of achieving an objective response (RR: 1.18; 95% CI: 0.72-1.95: I^2: 85%) or CR (RR: 1.51; 95% CI: 0.87-2.61; I^2: 79%) was not different between the two arms. Data available in 15 trials contributed to the network for PFS outcome while only eight trials contributed to OS outcome. Mixed treatment comparisons showed significantly improved PFS with nintedanib-gemcitabine-cisplatin (NinGC; HR: 0.42; 95% CI: 0.20-0.87) and dose-dense-methotrexate-vinblastine-doxorubicin-cisplatin (ddMVAC; HR: 0.61; 95% CI: 0.43-0.88) compared to LT only. Consistent benefit was observed when NinGC (HR: 0.48; 95% CI: 0.24-0.97) and ddMVAC (HR: 0.70; 95% CI: 0.51-0.96) were compared to GC only. However, no significant differences were observed between NinGC (rank 1) and ddMVAC (rank 2) or among other mixed treatment comparisons. Similarly, OS was significantly improved with NinGC (rank 1) relative to MVAC (HR: 0.41; 95% CI: 0.17-0.97), MVC (HR: 0.37; 95% CI: 0.16-0.88), MC (HR: 0.38; 95% CI: 0.16-0.92), AC (HR: 0.36; 95% CI: 0.15-0.91), and GC (HR: 0.39; 95% CI: 0.17-0.90). While similar results were observed with ddMVAC (rank 2) when compared to MVC (HR: 0.63; 95% CI: 0.42-0.94), MC (HR: 0.64; 95% CI: 0.42-0.98), and GC (HR: 0.66; 95% CI: 0.47-0.92), no significant differences were observed with ddMVAC when compared to MVAC (HR: 0.62; 95% CI: 0.38-1.01) and NinGC (HR: 1.70; 95% CI: 0.69-4.19). **Conclusions:** Current evidence shows improved PFS and OS with the use of neoadjuvant ddMVAC and Nin-GC in patients with MIBC relative to other treatment options. Research Sponsor: None.

Post hoc pooled analysis of first-line (1L) pembrolizumab (pembro) for advanced urothelial carcinoma (UC): Outcomes by response at week nine in KEYNOTE-052 and KEYNOTE-361.

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Background: Pembro is a 1L treatment for cisplatin-ineligible pts with UC. This post hoc landmark analysis evaluated clinical outcomes by response at 9 wk to 1L pembro monotherapy in pts with advanced/unresectable or metastatic UC from the single-arm phase 2 KEYNOTE-052 (NCT02335424) and the randomized phase 3 KEYNOTE-361 (NCT02853305) trials. **Methods:** Cisplatin-ineligible pts with advanced UC were enrolled in KEYNOTE-052 and received pembro (200 mg Q3W for ≤2 y). Platinum-eligible pts with advanced UC who had not previously received systemic chemotherapy (chemo) were enrolled in KEYNOTE-361 and randomly assigned 1:1:1 to receive pembro (200 mg Q3W for ≤2 y), pembro + chemo (1000 mg/m^2 gemcitabine on d1 and d8 + cisplatin [70 mg/m^2] or carboplatin [AUC 5] on d1 of each 3-wk cycle), or chemo. The primary analysis group included pembro monotherapy–treated pts; the sensitivity analysis group included pembro monotherapy–treated pts from KEYNOTE-052 and the choice of carboplatin subpopulation of pembro monotherapy–treated pts from KEYNOTE-361. Landmark analyses of OS by pts with CR, PR, SD, or PD per RECIST v1.1 by BICR at first imaging assessment (wk 9) were pooled for the ITT populations. Duration of CR/PR/SD and OS were estimated using the Kaplan-Meier method. Data cutoffs were Sep 26, 2020 (KEYNOTE-052) and Apr 29, 2020 (KEYNOTE-361). **Results:** The primary analysis group included 681 pembro-treated pts (KEYNOTE-052, N = 374; KEYNOTE-361, N = 307); the sensitivity analysis group included 544 pembro-treated pts (KEYNOTE-052, N = 374; KEYNOTE-361, N = 170). Median time from randomization to cutoff was 51.9 mo (range, 22.0-65.3) and 53.7 mo (range, 22.0-65.3) for the primary and sensitivity analysis groups, respectively. Twenty-five pts (4.6%) had CR and 135 (24.6%) had PR (primary group); 17 pts (3.9%) had CR and 105 (24.1%) had PR (sensitivity group). Median DOR was 25.9 mo for pts with CR/PR at wk 9; pts with CR/PR or SD at wk 9 had longer OS than pts with PD at wk 9 (Table). **Conclusions:** In this post hoc analysis, pts with advanced UC in KEYNOTE-052 and KEYNOTE-361 with CR/PR at wk 9 had better clinical outcomes with pembro monotherapy than pts with SD or PD; 1L pembro monotherapy continues to show efficacy in advanced UC. Clinical trial information: NCT02335424 and NCT02853305. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Pooled outcomes by response at week nine. Primary Analysis	CR/PRn = 160	SDn = 154	PDn = 234
Median OS from wk 9, mo (95% CI)	51.4 (36.9-NR)	17.5 (14.5-24.7)	5.9 (5.0-7.2)
36-month OS rate from wk 9, % (95% CI)	62.5 (54.0-69.9)	28.5 (21.1-36.3)	4.8 (2.4-8.4)
Duration of CR/PR/SD, median (range), mo	25.9 (0.0-60.7+)	4.2 (0.0-51.5+)	NA
Sensitivity Analysis	**n = 122**	**n = 125**	**n = 188**
Median OS from wk 9, mo (95% CI)	50.7 (36.2-NR)	17.5 (13.3-24.7)	5.3 (4.0-6.5)
36-month OS rate from wk 9, % (95% CI)	60.7 (51.1-68.9)	29.2 (21.1-37.8)	4.9 (2.3-8.8)
Duration of CR/PR/SD, median (range), mo	26.2 (0.0-60.7+)	4.2 (0.0-51.5+)	NA

Survival outcomes with radical cystectomy (RC) in localized clinically node-positive bladder cancer (CNBC).

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Background: The role of RC in patients with CNBC remains unclear since most prospective clinical trials excluded them. Our study aims to evaluate overall survival (OS) in patients with CNBC treated with systemic chemotherapy (SC) with or without RC. **Methods:** We queried the National Cancer Database for adult patients who received SC for localized CNBC during the years 2004 to 2018. Patients with distant metastases, including to non-regional nodes, and those treated with radiation to the bladder or pelvic nodes were excluded. Chi-square and Mann Whitney U tests were used to compare frequency distributions. Cox proportional hazards analysis was employed for multivariate analysis of factors associated with OS. **Results:** A total of 8464 patients were identified – 3565 (42.1%) underwent RC + SC (RC^+), while 4899 (57.9%) received only SC (RC^-). Median age at diagnosis was 65y in the RC^+ grp vs. 68y in the RC^- grp ($P = 0.006$). Majority of patients were Caucasian in both grps – 86.9% and 85.1%, respectively. 5y-OS was 34.1% in the RC^+ grp vs. 36.1% in the RC^- grp ($P = 0.06$). On multivariate analysis, factors independently associated with OS were RC^+ status (Hazard ratio (HR) 0.81, 95% CI 0.75-0.88, $P < 0.001$), advanced age (70-85y vs. 18-35y, HR 1.88, 95% CI 1.18-3.01, $P < 0.001$), female gender (HR 1.20, 95% CI 1.12-1.28, $P = 0.001$), African American (vs. Caucasian) race (HR 1.24, 95% CI:1.10-1.40, $P = 0.0004$), ≥ 2 comorbidities (HR 1.67, 95% CI 1.34-1.92, $P = 0.001$), annual income ($<$ \$30,000 vs $>$ \$45,000, HR 1.24, 95% CI 1.13-1.37, $P < 0.001$), and insurance status (uninsured vs. private, HR 1.39, 1.15-1.67, $P < 0.001$). **Conclusions:** In this large retrospective analysis, among patients with localized CNBC who received SC, 5y-OS rates were comparable with or without RC. However, RC was associated with improved OS on multivariate analysis. Research Sponsor: None.

Variable	Univariate HR for mortality (95% CI)	p-value	Multivariate HR for mortality (95% CI)	p-value
RC^+ vs. RC^-	0.90 (0.84-0.95)	0.001	0.81 (0.75-0.88)	< 0.001
Age group (70-85 vs. 18-35y)	1.80 (1.36-2.39)	0.001	1.88 (1.18-3.01)	< 0.001
Female gender	1.21 (1.13-1.29)	0.001	1.20 (1.12-1.28)	0.001
AA vs. White	1.36 (1.21-1.52)	0.001	1.24 (1.10-1.40)	0.0004
≥2 vs. 0 comorbidities	1.80 (1.49-2.17)	0.001	1.67 (1.34-1.92)	0.0001
Uninsured vs. Private insurance	1.43 (1.19-1.72)	0.001	1.39 (1.15-1.67)	0.001
Median annual income < \$30,000 vs. > \$46,000	1.38 (1.26-1.52)	0.001	1.24 (1.13-1.37)	0.001

First-line pembrolizumab in advanced urothelial carcinoma: Clinical parameters associated with efficacy in the phase 2 KEYNOTE-052 and phase 3 KEYNOTE-361 trials.

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Background: First-line treatment with pembrolizumab (pembro) monotherapy has shown durable clinical activity in selected patients (pts) with advanced/unresectable or metastatic urothelial carcinoma (UC). In a pooled population of pts with advanced UC from the single-arm phase 2 KEYNOTE-052 (NCT02335424) and the randomized, open-label, phase 3 KEYNOTE-361 (NCT02853305) studies, this exploratory analysis evaluated the relationship between baseline characteristics and clinical outcomes of first-line pembro monotherapy. **Methods:** Cisplatin-ineligible pts with advanced UC were enrolled in KEYNOTE-052 and chemotherapy-naive pts with advanced UC were enrolled in KEYNOTE-361. For analysis of predictive factors for ORR and OS in pembro-treated pts, the purposeful selection method was used to build the multivariable logistic regression model (ORR) and multivariable Cox model (OS), beginning with a univariable analysis of each independent variable. Any variable in the univariate model with $P < 0.10$ was a candidate for the multivariate model. The stepwise selection method was used to select the variables in the final model. Significance of the final model was set at $P < 0.05$. Data cutoff dates were September 26, 2020 (KEYNOTE-052) and April 29, 2020 (KEYNOTE-361). **Results:** This pooled analysis included 681 pts treated with pembro monotherapy (KEYNOTE-052, N = 374; KEYNOTE-361, N = 307 [170 were cisplatin ineligible]). Median follow-up was 51.9 mo (range, 22.0-65.3). ORR was 29.4% (95% CI, 26.0-32.9; 69 CRs, 131 PRs), and median DOR was 33.2 mo (range, 1.4+ to 60.7+). Median OS was 12.5 mo (95% CI, 11.0-14.6). By multivariate analysis, independent factors significantly associated with higher ORR were PD-L1 status (combined positive score [CPS] ≥10 vs CPS < 10; odds ratio [OR], 1.90 [95% CI, 1.33-2.71]; $P = 0.0004$), site of metastasis (lymph node only vs visceral disease; OR, 1.66 [95% CI, 1.06-2.59]; $P = 0.0265$), liver involvement (absent vs present; OR, 1.75 [95% CI, 1.06-2.89]; $P = 0.0294$), and baseline hemoglobin level ≥10 vs < 10 g/dL; OR, 2.17 [95% CI, 1.09-4.31]; $P = 0.0276$). Multivariate analysis of OS is displayed in the Table. **Conclusions:** This exploratory multivariate analysis identified numerous factors, including PD-L1–positive status (CPS ≥10), lymph node only metastasis, and lower ECOG PS score, associated with improved clinical outcomes in pts with advanced UC treated with first-line pembro monotherapy. Clinical trial information: NCT02335424 and NCT02853305. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Factor and Comparison	OSHR (95% CI)	*P* Value
Age: < 65 years vs ≥65 years	0.78 (0.63-0.97)	0.0274
PD-L1: CPS ≥10 vs CPS < 10	0.73 (0.61-0.89)	0.0014
Site of metastasis: lymph node only vs visceral disease	0.71 (0.55-0.91)	0.0074
Baseline tumor volume: < median vs ≥ median	0.64 (0.53-0.77)	< 0.001
Baseline hemoglobin: ≥10 vs < 10 g/dL	0.54 (0.41-0.70)	< 0.001
ECOG PS score		< 0.001
0 vs 1	0.67 (0.53-0.84)	
0 vs 2	0.58 (0.45-0.73)	
1 vs 2	0.86 (0.70-1.07)	

Defining innate immune training potential as a predictor of Bacillus Calmette-Guérin immunotherapy response in nonmuscle-invasive bladder cancer.

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Background: Intravesical instillation of the live attenuated mycobacterium Bacillus Calmette-Guerin (BCG) remains the most effective therapy for the treatment of non-muscle invasive bladder cancer. The precise mechanism of BCG is thought to involve phagocytosis, induction of inflammation, activation of the innate immune apparatus, and an effective cell-mediated T cell response. An increasing body of evidence suggests that the innate immune system has characteristics that involve a heterologous memory of past insults through a process thought to involve epigenetic reprogramming, termed trained immunity. We seek to investigate the potential for innate immune training as a predictor of the anti-tumor effects of BCG. **Methods:** A prospective biospecimen collection was performed on venous blood from non-muscle invasive bladder cancer patients prior to receiving intravesical BCG therapy. To investigate the role of trained immunity in primary monocytes, cells were isolated from peripheral blood mononuclear cells (PBMC) by plate adhesion. 2-5 x 10^5 cells/well were assayed in 96-well format, cultured in RPMI 1640 supplemented with 10% Fetal Bovine Serum and 2mM L-glutamine and stimulated with 10:1 MOI BCG for 24 hours. Cells were then washed in media and allowed to rest 6 days. Media was changed on day 3 of rest. Subsequently, cells were stimulated with 25 ng/ml lipopolysaccharide (a TLR4 agonist) for 24 hours. Cell free supernatant was measured for TNF-alpha production by enzyme-linked immunosorbent assay. **Results:** In vitro training of primary monocytes induced an increase in proinflammatory cytokine production upon re-stimulation. This phenotype was dose dependent on stimulation with LPS, however, the relative change between trained and untrained cells was diminished at higher concentrations of agonist. In our in vitro training experiments, there was demonstrable interpatient variability seen pre-BCG exposure in a cohort of NMIBC patients. These results will be correlated with future long term BCG response in this prospective cohort. **Conclusions:** We present data on a trained innate immune phenotype on primary monocytes collected from patient samples. These data serve as proof of principle for the ability to induce a trained phenotype in vitro. These findings will be correlated with prospective clinical data on BCG responsiveness and recurrence free survival to allow us to garner further insight into the role of trained immunity in BCG immunotherapy. Such insight will have potential clinical impact on the development of biomarkers and clinical assays that could predict immune responsiveness to BCG a priori, as well as identify possible immunological adjuvants that could enhance the effect of intravesical BCG. Research Sponsor: U.S. National Institutes of Health.

523 **Poster Session**

Defining hereditary upper tract urothelial carcinoma: Implications for genetic testing and clinical management.

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Background: Despite being a rare cancer, upper tract urothelial carcinoma (UTUC) is the third most common core cancer associated with Lynch syndrome (LS) after colorectal and endometrial cancers. Yet, there is no established guideline to identify patients with UTUC who are at risk of carrying germline mutations in LS-associated genes. The objective of this study is to define selection criteria for patients with UTUC for LS screening. **Methods:** We retrospectively identified patients with UTUC who underwent germline sequencing of ≥77 cancer susceptibility genes using next generation sequencing (NGS) as part of a prospective matched tumor-normal genomic profiling initiative from 04/2015 to 04/2021. Mismatch repair protein status was evaluated by immunohistochemical (IHC) staining for MMR genes *MSH2*, *MSH6*, *MLH1*, and *PMS2*. Microsatellite instability (MSI) status was determined using NGS. Diagnostic performance of clinical and tumor-based screening criteria was assessed by the presence of germline pathogenic/likely pathogenic variants (PGVs) in MMR genes. **Results:** A total of 232 patients with UTUC underwent germline testing; median age of diagnosis was 67 years (interquartile range 59 – 73). Of these patients, 70% were male, 43% had UTUC diagnosed before the age of 65, 85% had high grade UTUC,12% had bilateral UTUC, 11% had metastasis at diagnosis, 10% and 31% had personal and family history of LS-associated cancers, respectively. PGVs in moderate or high-penetrance genes were identified in 31 (13%) patients including 6 (3%) in *BRCA1/2* and 21 (9%) in MMR genes (13 *MSH2*, 4 *MSH6*, 4 *MLH1*). A total of 10/21 (48%) patients with MMR PGVs developed UTUC as their first cancer diagnosis. Of patients with MMR PVGs, 15/16 (94%) had MMR-deficient tumors and 12/18 (67%) had MSI-high tumors. Personal and family history of LS core cancers ($p < 0.001$), age of diagnosis < 65 ($p = 0.008$), MSI-high ($p < 0.001$), and MMR-deficiency ($p < 0.001$) were associated with MMR carrier status. Female gender ($p = 0.7$), HG UTUC ($p = 0.5$), and bilateral UTUC ($p = 0.7$) were not associated with MMR PGVs. Current NCCN genetic referral criteria for Lynch syndrome has high specificity in identifying patients with LS (100%) but missed 11/21 (52%) patients with UTUC and MMR PGVs. **Conclusions:** Current genetic referral guidelines for Lynch syndrome may miss a significant portion of patients with LS-associated UTUC. UTUC tumor should be investigated for MMR protein and MSI status with IHC or next generation sequencing methods to augment LS-screening of patients with UTUC and inform systemic treatment selection. Research Sponsor: U.S. National Institutes of Health.

Impact of different HER2 expression levels on the outcomes of second-line immunotherapy for metastatic urothelial carcinoma.

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Background: Immunotherapy has become an option of second-line treatment for metastatic urothelial carcinoma (mUC) after the failure of platinum-containing chemotherapy. HER2 expression is an adverse prognostic factor of urothelial carcinoma (UC) while the predictive value of HER2 expression in UC treatment remains unknown. This study attempts to explore the impact of different HER2 expression and gene amplification levels on the outcomes of second-line immunotherapy in metastatic UC. **Methods:** The baseline clinical data and the outcomes after second-line anti-PD-1 immunotherapy from 2017 to 2021 in 79 patients with metastatic UC who failed to the first-line platinum-containing chemotherapy were reviewed. The expression level of HER2 was detected by immunohistochemistry (IHC) staining (Anti-Her2/neu, Cat.4B5, Ventana) from formalin-fixed paraffin-embedded (FFPE) tumor tissue of patients. The copy number amplification level of HER2 gene was detected by second-generation sequencing (NGS) from FFPE tumor tissue of patients. The correlation between HER2 expression and objective response rate (ORR), median progression-free survival (PFS) and overall survival (OS) were analyzed. **Results:** HER2 expression levels by IHC were performed in 77 patients and the copy number (CN) amplification level of 20 patients with HER2 IHC 2+ were detected by NGS. The median PFS of HER2 negative (IHC 0), low expression (IHC 2 +/ CN - and IHC 1 +) and overexpression (IHC 3 + and IHC 2 +/ CN +) patients were 11.0 months (95% confidence interval [CI]: 1.4-20.6 months), 3.7 months (95% CI: 1.3-6.1 months) and 1.8 months (95% CI: 0.8-2.8 months), respectively, with significant difference in the overall comparison ($P = 0.001$) and in the each two comparisons. ORR had a trend to decrease gradually with the increase of HER2 expression level from negative to overexpression (42.4% vs. 31.6% vs. 0%, $P = 0.08$). However, no correlation between HER2 expression and OS after anti-PD-1 immunotherapy was observed. **Conclusions:** Different HER2 expression levels have a significant impact on the PFS of the second-line anti-PD-1 immunotherapy in patients with metastatic urothelial carcinoma. The overexpression of HER2 (IHC 3 + and IHC 2 +/ CN +) may be an adverse factor, while the HER2-negative status may be a favorable factor. HER2 expression have potential value in predicting the efficacy of second-line immunotherapy for advanced urothelial carcinoma, which needs further research. Research Sponsor: National Natural Science Foundation of China (NO.82172604).

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Actionable genomic landscapes from a real-world cohort of localized urothelial carcinoma patients.

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Background: Recent targeted therapies for advanced and metastatic urothelial cancer have generated enthusiasm, but the actionable genomic landscape of early-stage disease remains largely unknown. Here, we used real-world evidence to investigate differences between somatic and germline mutations in localized, early-stage urothelial cancers and advanced urothelial cancers. **Methods:** We retrospectively analyzed de-identified NGS data from 1,146 bladder cancer patients (stages I-IV) with formalin-fixed, paraffin-embedded tumor biopsies sequenced using the TempuslxT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage; whole-exome capture RNA-seq). For the subset of patients with tumor-normal match sequencing (n=758), additional incidental germline alterations in 46 different genes were assessed. **Results:** A total of 1,146 bladder cancer tumors were investigated: stage I-II (n=124), stage III (n=159), and stage IV (n=863)—summarized in Table. Tumor mutational burden (TMB) was calculated for 1,126 tumors, and TMB-high (TMB-H; ≥10 mutations per megabase) was similar across tumor stages. PD-L1 immunohistochemical staining was performed on 698 tumors, and no significant differences were observed. Microsatellite instability high (MSI-H) status was detected in only 2 (1.6%) stage I-II tumors and 8 (0.9%) stage IV tumors. Alterations—single nucleotide variants, insertions/deletions, and copy number variants—in *FGFR2/3*, homologous recombination repair genes (18 genes including *BRCA1/2* and *ATM),* additional DNA repair gene mutations (*ERCC2, RB1, FANCC)* and *NTRK* fusions were detected at similar frequencies across disease stages. In 758 patients with tumor/normal matched sequencing, we identified a low rate of incidental germline mutations in *MUTYH* (stage III, 1%; stage IV, 1.9%), *BRCA2* (stages I-II, 1.2%; stage III, 1%; stage IV, 0.5%), *BRIP1* (stages I-II, 1.2%), *ATM* (stage III, 1%; stage IV, 0.7%), *MSH6* (stage III, 1%; stage IV, 0.2%), and *TP53* (stage III, 1%; stage IV, 0.2%). **Conclusions:** Patients with bladder cancer have similar rates of potentially actionable mutations and genomic landscapes regardless of clinical disease stage. These findings provide a rationale for further investigating targeted therapies among early-stage bladder cancer patients. Research Sponsor: None.

Biomarker and Somatic Alterations		Stages I-II (n=124)	Stage III (n=159)	Stage IV (n=863)	p-value
TMB-H		34/124 (27.4%)	33/155 (20.8%)	183/847 (21.2%)	0.33
MSI-H		2/124 (1.6%)	0/157 (0%)	8/857 (0.9%)	0.34
PD-L1 Positive		31/82 (37.8%)	47/113(41.6%)	168/503 (33.4%)	0.23
FGFR2/3 Mutations/Fusions		22 (17.7%)	28 (17.6%)	158 (18.3%)	>0.99
HRR Gene Mutations		23 (18.5%)	28 (17.6%)	158 (18.3%)	0.97
Additional DNA Repair Genes	*ERCC2*	3 (2.4%)	3 (1.9%)	11 (1.3%)	0.45
	RB1	20 (16.1%)	36 (22.6%)	152 (17.6%)	0.26
	FANCC	0 (0%)	0 (0%)	3 (0.3%)	>0.99
NTRK1/2/3 Fusion		0 (0%)	0 (0%)	2 (0.2%)	>0.99

Immunological correlates of response and immune-mediated toxicity in checkpoint inhibitor (ICI)-treated metastatic urothelial carcinoma (mUC) patients (pts).

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Background: Myeloid derived suppressors cells (MDSC) are immune cells that create an immunosuppressive microenvironment. Increased expression of MDSC subsets is associated with worse overall survival in ICI-treated mUC pts, but their role in immune-related adverse events (irAE) is unknown. Immune profiles associated with irAE are also unknown. We investigated associations of MDSC and –omics profiles with response and irAE in ICI-treated mUC pts. **Methods:** Baseline (B) and on-treatment (Tx) blood samples were collected from ICI-treated mUC pts. MDSC were measured in fresh unfractionated whole blood (WB) and in peripheral blood mononuclear cells (PBMC). MDSC were identified by flow cytometry in WB, defined as LinloCD33+/HLADR-, and subclassified as polymorphonuclear (PMN)-MDSC (CD15+/CD14-), monocytic (M)-MDSC (CD15-/CD14+), and uncommitted (UC)-MDSC (CD15-/CD14-). MDSC populations were presented as % of live nucleated blood cells and as absolute numbers from WB. irAE severity was graded by CTCAE v5. In a subcohort of 17 pts, proteomics and transcriptomics were analyzed via Olink and Bulk RNAseq, respectively. Wilcoxon rank sum test compared MDSC and –omics among response and irAE groups. Kruskal-Wallis test compared –omics results between irAE responders (irAE-R), irAE non-responders (irAE-NR), and no irAE/non-responders (noAE-NR). **Results:** 41 ICI-treated mUC pts (25 anti-PD-L1, 16 anti-PD-1) had at least 1 MDSC sample: 28 pts at B, 30 pts at Tx, and 17 pts at both B and Tx. Primary UC sites were bladder (78%) and upper tract (22%); 73% male; median age 72 (range, 28-82); 85% had KPS $>$ 80%; 51% had visceral metastasis. ICI was first and second-line therapy in 37% and 63% of pts, respectively. 13 pts were responders (R); 26 pts were non-responders (NR); 2 pts were not evaluable. 22 pts developed irAE. Median time to irAE was 84 days (range, 21-145); 10 pts required steroids; 3 required ICI discontinuation. UC-MDSC was predominant in WB and PMN-MDSC in PBMC in both B and Tx. Between B and Tx, WB UC-MDSC and PB UC-MDSC increased in R (n = 13; p = 0.04), but decreased in NR (n = 26; p = 0.02). In the subcohort of 17 pts, 11 had irAE (7 irAE-R; 4 irAE-NR), 6 had noAE-NR. Proteomic analysis showed increased expression of CXCL12 in noAE-NR pts (p = 0.006) and increased expression of IL-8 (p = 0.016), IL-18 (p = 0.012), and IL-18R1 (p = 0.016) in all irAE pts. At the transcriptome level, upregulation of IFN-γ was associated with response, whereas upregulation of both IFN-γ and IFN-α differentiated irAE-R from irAE-NR. **Conclusions:** In ICI-treated mUC pts, WB & PB UC-MDSC increased in R and decreased in NR between B and Tx. Increased expression of pro-inflammatory chemokines was observed in irAE pts, independent of response. A distinct inflammatory pathway was observed in irAE-R. Prospective investigation of blood-based biomarkers of response and irAE development is warranted. Research Sponsor: Cleveland Clinic Urologic Oncology Departmental Fund.

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Characterizing molecular subtypes of high-risk nonmuscle-invasive bladder cancer in African American patients.

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Background: Patients with high-risk non-muscle-invasive bladder cancer (NMIBC) have heterogeneous outcomes with African Americans (AAs) having worse survival than European Americans (EAs). It is unknown whether race-based biological differences contribute to this disparity. **Methods:** We performed a retrospective cohort study including patients from the University of Texas Medical Branch (UTMB) and the Durham VA Health Care System (DVAHCS) from 2010-2020 among treatment naïve, high-risk NMIBC. Profiled gene expressions of high-risk NMIBC by race were performed using the UROMOL classification system. **Results:** A total of 26 patients (14 AAs and 12 EAs) matched on age and sex were included with no significant difference in clinical stage group (CIS +/- T1 or TaHG vs. TaHG or T1, no CIS), smoking status, or progression. We found a similar racial UROMOL subtype distribution with class 2a being most common. A total of 10 genes were discovered to be commonly upregulated differentially expressed genes (up-DEGs) in AAs vs EAs. EFEMP1, which has been associated with progression to muscle-invasive bladder cancer (MIBC) in vitro, and S100A16 gene expression, which has been implicated with mitomycin C resistance in bladder cancer in vitro, was significantly more common among AAs. We used single nuclei analysis to map the malignant cell heterogeneity in urothelial cancer which five distinct malignant epithelial subtypes whose presence has been associated with different therapeutic response prediction ability. We mapped the expression of the 10 genes commonly up-DEGs by race as a function of the five malignant subtypes. This showed borderline ($p = 0.056$) differences among the subtypes suggesting AA and EA patients may be expected to have different therapeutic responses to treatments for BC. AAs were enriched with immune-related, inflammatory, and cellular regulation pathways compared to EAs, yet appeared to have reduced levels of the aggressive C3 bladder tumor cell population. **Conclusions:** In this small sample, we found similar subtype distribution among high-risk NMIBC patients according to race. However, gene expression differs by race, supporting potential novel race-based etiologies for differences in muscle-invasion, response to treatments, and transcriptome pathway regulations. Further biological studies in NMIBC molecular sub-stratification, associated treatment(s), and prognoses in a larger cohort are needed to support these hypotheses. Research Sponsor: Department of Defense Peer Reviewed Cancer Research Program (PRCRP) Career Development Award., U.S. National Institutes of Health., The University of Texas Medical Branch Department of Surgery Seed Grant, National Institute of Health Loan Repayment Program, UTMB Clinical and Translational Science Award.

Biomarker analysis and updated clinical follow-up from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in patients with muscle-invasive bladder cancer (MIBC) undergoing cystectomy.

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Background: The BLASST-1 study is multi-center phase II trial evaluating the combination of nivolumab (N) with gemcitabine-cisplatin (GC) as a neoadjuvant therapy for patients (pts) with MIBC undergoing radical cystectomy (RC). The primary endpoint was pathologic down staging (PaR; ≤pT1N0). Safety, Relapse-free survival (RFS), Progression-free survival (PFS) and biomarker analyses were secondary endpoints. We previously reported a PaR rate of 65.8% and pCR rate of 49%. There were no safety concerns or delays to surgery. (ASCO GU 2020) Here, we correlate PaR with biomarkers (Tumor mutational burden (TMB), PD-L1 and molecular subtypes) and provide updated clinical follow-up (FU) data. **Methods:** Forty-one pts with MIBC (cT2-T4a, N≤1, M0) and candidates for RC were enrolled between Feb 2018 and June 2019; (cT2N0 90%, cT3N0 7%, cT4N1 3%). Pts received C (70mg/m2) IV on D1, G (1000mg/m2) on D1, D8 and N (360 mg) IV on D8 every 21 days for 4 cycles followed by RC within 8 weeks. For RNA-based analysis, GeneChip Human Exon 1.0 ST Array (Affymetrix) was used; baseline tumors from 37 patients passed quality control and had available transcriptome data. A cohort (n=223) of patients treated with NAC+RC was used as a comparator for molecular subtyping analysis. DNA was extracted from baseline pre-treatment tumor samples and sequenced to an average depth of 150X and the DNA extracted from matched normal tissue (peripheral blood) to a mean depth of 50X. PD-L1 expression was assessed using IHC 28-8 antibody on baseline tumors. **Results:** At a median FU of 15.8 months,12-month RFS rate was 85.4% and PFS including death from any cause was 83%. There were no long-term safety concerns. Molecular subtyping found patients with a basal-type tumor (Basal or Claudin-low) had a more favorable overall PaR in 13/18 = 73% with PaR in 9/13 in basal (69%) and 4/5 in claudin-low (80%) compared to overall PaR of 58% for the luminal-type tumors (Luminal or Infiltrated luminal) with a breakdown of PaR in 5/8 (63%) in luminal and 6/11 (54%) in infiltrated luminal. In contrast, in the comparator NAC cohort, the PaR rates were similar for basal-type and luminal-type tumors, with 44% and 48% respectively. There was no correlation of PaR with TMB or PD-L1 expression from bassline pre-treatment tumors. Biomarker analyses from residual tumors in RC tissues are ongoing. **Conclusions:** The combination of N+GC was safe and efficacious in MIBC with encouraging outcomes of pathologic down staging and relapse-free survival at a median FU of 15.8 months. Molecular subtyping results suggest basal-type tumors may respond more favorably to this chemo-immunotherapy treatment regimen. Clinical trial information: NCT03294304. Research Sponsor: Bristol Meyers Squibb.

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Expression of Nectin-4 and PD-L1 in bladder cancer with variant histology.

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Background: Nectin-4, a cell adhesion molecule found in a frequently amplified region of the bladder cancer (BC) genome, has been recently used as target for the systemic treatment of locally advanced or metastatic BC. BC with variant histology (BCVH) is associated with poor clinical outcomes, and there is an unmet need for novel treatments in this population. Little is known about Nectin-4 expression and other targets. We investigated Nectin-4 and programmed death-ligand 1 (PD-L1) expression in BCVH. **Methods:** We performed a retrospective analysis of 117 patients with BCVH whose samples were collected at Winship Cancer Institute of Emory University from 2011-2021. Immunohistochemistry (IHC) was performed for Nectin-4 and PD-L1 expression on formalin-fixed, paraffin-embedded (FFPE) tissue. Nectin-4 staining was performed by Q2 Solutions using non-commercially available anti-Nectin-4 antibody (clone M22-312B41.1). Expression was measured using the H-score method (H-score = [% of strong positive tumor cells $\times$ 3] + [% of moderate positive tumor cells $\times$ 2] + [% of weak positive tumor cells $\times$ 1]). PD-L1 levels were assessed in tumor-infiltrating immune cells using DAKO 22C3 IHC to determine PD-L1 high, defined by a Combined Positive Score (CPS) of $\geq$10. **Results:** Median age was 70 years (mean=67.2, range 22-91), with 61.5% male, 54.7% white, and 32.5% black. Nearly all samples were taken from the bladder (95.7%), with 4.3% from sites of metastasis. The most common histologic variant was squamous cell carcinoma (26.5%), and the distribution of variants is summarized in table. Nectin-4 staining was successfully performed on 111 samples, and PD-L1 staining on 116. Nectin-4 expression was seen across different histological subtypes (mean H-score: 153.1, median [range]: 157 [0-300]), with highest expression in plasmacytoid and squamous, and lowest expression in small cell and sarcomatoid (Table). More than one-third (35.3%) were PD-L1 high, and greater in sarcomatoid and squamous cell histology (70.8% and 50% positivity, respectively). Only 5% of plasmacytoid samples were PD-L1 high. **Conclusions:** Although there is heterogeneity, our results showed expression of Nectin-4 and PD-L1 in this cohort of patients with BCVH. These findings highlight the therapeutic potential of antibody-drug conjugates against Nectin-4- and anti PD1/PD-L1-based therapy in this population. Additional analysis including clinical outcomes and genomic analyses are ongoing, and a prospective clinical trial is planned. Research Sponsor: Astellas Pharma Global Development, Inc./Seagen.

Nectin-4 and PD-L1 staining results among BCVH subtypes.

			Nectin-4 H-score		PD-L1
Histology	**No. of specimens**	**% of total (N = 117)**	**Mean**	**Median (range)**	**CPS≥10 n(%)**
Squamous	31	26.5	207.7	219.5 (17-300)	15/30 (50)
Adenocarcinoma	24	20.5	166.9	140.0 (45-299)	4/24 (16.7)
Sarcomatoid	24	20.5	52.3	2.5 (0-300)	17/24 (70.8)
Plasmacytoid	20	17.1	253.5	257.5 (108-300)	1/20 (5)
Small cell	10	8.5	46.8	0 (0-233)	2/10 (20)
Mixed	8	6.8	122	105 (20-265)	2/8 (25)

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Prognostic value and therapeutic implications of an integrative molecular subtype and immune content classifier in localized muscle-invasive bladder cancer.

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Background: Localized muscle-invasive bladder cancer (MIBC) exhibits heterogeneous molecular features and outcomes, with a 5-year mortality rate of approximately 30%. Immune checkpoint blockade (ICB) has the potential to improve oncological outcomes but molecular tools are needed to identify those most likely to benefit. Here, we integrate transcriptomically derived tumor immune microenvironment (TIME) data with molecular subtypes to create a novel integrative classifier with prognostic and therapeutic implications. **Methods:** RNAseq data from patients with localized muscle-invasive bladder cancer (MIBC) from the Cancer Genome Atlas BLCA (TCGA-BLCA) project was utilized (n = 187). CIBERSORT was used for immune cell deconvolution, and unsupervised hierarchical clustering divided the cohort based on similar immune profiles. Consensus molecular clustering information for the cohort was obtained from Kamoun et al. Overall survival (OS) of each cluster were analyzed. The tumor immune dysfunction and exclusion (TIDE) tool, which uses a genomic signature validated on immunotherapy treated melanoma patients to model tumor immune evasion, was then used to predict response to ICB. **Results:** In the TCGA-BLCA cohort, there were two distinct clusters enriched with macrophages, CL1-M0^{Hi} (n = 18) and CL5-M2^{Hi} (n = 35). Compared to the rest of the cohort, these two macrophage enriched clusters combined exhibited a decreased OS (33.1 mo vs. NR, p = 0.01). TIDE tool predicted ICB response was lowest in CL1 (6/18, 33%; p = 0.09), CL5 (12/35, 34%; p = 0.02), and the Ba/Sq molecular cluster (16/57, 28%; p = $1.3x10^{-5}$). Patients designated as CL1 or CL5 by immune clustering and Ba/Sq by molecular consensus were combined into a subgroup (n = 20). Compared to the rest of the cohort, this Ba/Sq_Macrophage^{Hi} subgroup had a higher body mass index (31.0 vs. 25.8 BMI, p = 0.0004), more whites (95% vs. 64%, p = 0.03), and had a higher stage (80% Stage III/IV vs. 20% Stage I/II, p = 0.05). The Ba/Sq_Macrophage^{Hi} cluster demonstrated higher PD-L1 expression (mean Z score 0.15 vs. -0.09; p = 0.008), there was a higher degree of T cell exclusion (mean Z score 0.16 vs. -0.06; p = 0.003) and cancer-associated fibroblasts (mean Z score 0.03 vs. -0.02; p = $3.4x10^{-5}$). Overall, the predicted response to ICB by TIDE in the Ba/Sq_Macrophage^{Hi} was lower (OR 0.15, 0.03-0.55 p = 0.002) and OS was significantly shorter (median 16.7 mos vs. 54.9 mo, p = 0.04). **Conclusions:** We demonstrated the prognostic significance of the Basal/Squamous subtype with macrophage enrichment in patients with localized MIBC. Pending further prospective validation, this sub-population may be less amenable to ICB treatment. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

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Biomarkers predictive of response to enfortumab vedotin (EV) treatment in advanced urothelial cancer (aUC).

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Background: EV is an antibody-drug conjugate which recently received full FDA approval for treatment-refractory aUC. Molecular biomarkers and characteristics of patients (pts) most likely to respond to EV therapy have not been well defined. **Methods:** We retrospectively identified all aUC pts treated with EV at our institution. Clinicopathologic, treatment and response data were abstracted from pt charts. Pts were considered responders to EV if they had a complete response on initial scans after 2-3 months of treatment, or were treated with EV for $\geq$ 6 months. Responders and non-responders were compared in terms of their molecular and clinical characteristics using Chi-squared test. Most common somatic alterations present in $\geq$10 pts (*TERTp*, *TP53*, *CDKN2A*, *CDKN2B*) were also used to divide pts with available next-generation sequencing (NGS) results into groups with and without these alterations. Log rank test was used to determine differences in overall survival (OS) and progression free survival (PFS) among these groups. **Results:** Between 1/2020 and 8/2021 a total of 32 pts received EV and 28 had NGS data available with either FoundationOne (14 pts), UCSF500 (13 pts) or Strata (1). Median age was 69.5 years, 24 (75%) were male, 22 (69%) Caucasian, 22 (69%) had pure urothelial histology and 22 (69%) primary tumor location in the bladder. At EV start, 24 (75%) had visceral metastases (mets), 8 (25%) had liver mets, and 13 (41%) had bone mets. Median follow-up from EV start was 12.5 months (range 0.5-36); 20 (63%) pts received EV monotherapy, and 12 (37%) received EV as part of a combination regimen. Non-responders were more likely to have bone metastases (69% vs 21%, $p<0.01$), but were otherwise similar in baseline clinical characteristics to responders. *TP53* alterations were enriched in responders relative to non-responders, whereas non-responders had more *CDKN2B* alterations (Table). Similar findings were seen in the subset of pts treated with EV monotherapy. Pts with *TP53* alterations had longer OS (NR vs 17.0 months, p=0.06) and PFS (NR vs 6.6 months, p=0.04) relative to wild-type pts. Shorter PFS was seen in pts with *CDKN2A* (4.4 months vs NR, p=0.05) and *CDKN2B* (4.3 months vs NR, p=0.02) alterations, but no differences in OS were observed. **Conclusions:** In this retrospective cohort of aUC pts with available NGS data, presence of *TP53* and absence of *CDKN2A* and *CDKN2B* alterations were associated with favorable responses and improved clinical outcomes with EV, suggesting they may be biomarkers of response to EV. These preliminary findings should be validated in larger cohorts. Research Sponsor: None.

Alteration	Responders (N = 17)	Non-Responders (N=11)	p-value	Monotherapy responders (N=8)	Monotherapy Non-Responders (N=10)	p-value
***TERT* (N=19)**	11 (65%)	8 (73%)	0.65	6 (75%)	7 (70%)	0.81
***TP53* (N=16)**	12 (71%)	4 (36%)	0.07	6 (75%)	3 (30%)	0.06
***CDKN2A* (N=11)**	5 (29%)	6 (55%)	0.18	2 (25%)	5 (50%)	0.28
***CDKN2B* (N=10)**	4 (24%)	6 (55%)	0.09	1 (13%)	5 (50%)	0.09

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Serial ctDNA evaluation to predict clinical progression in patients with advanced urothelial carcinoma.

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Background: It is not known whether serial circulating tumor DNA (ctDNA) can augment imaging for assessing treatment response in patients (pts.) with advanced urothelial carcinoma (UC). We hypothesized that serial ctDNA measurements predict the clinical progression of advanced UC and map its evolutionary trajectories. **Methods:** We analyzed 182 serial ctDNA samples from 53 pts. with advanced UC sequenced by the Guardant360 ctDNA platform. The aggregate variant allele frequency (aVAF) was defined as the sum of VAFs of all genomic alterations (GAs) in a ctDNA sample. Clinical response status was categorized into progressive disease (PD) and non-PD based on imaging. Progression-free survival (PFS) was defined as the time from treatment start till PD or death. The Mann-Whitney test was used to compare radiologic response status (PD vs. non-PD) and the ctDNA aVAF collected within 4 weeks of restaging imaging. **Results:** Pts. with lower initial ctDNA aVAF ($\leq$0.2) had longer overall survival (OS) (hazard ratio (HR): 0.31, 95%CI: 0.11-0.90, p = 0.03). Pts. who achieved clearance of their ctDNA aVAF at the time of any subsequent ctDNA sample (n = 19/53) had longer OS (HR: 0.26, 95%CI: 0.08-0.85, adjusted p = 0.027). Combining ctDNA aVAF values from two consecutive samples improved the performance of a clinical prognostic model based on age, sex, and liver metastasis (C-statistic improved from 0.65 to 0.84). The mean ctDNA aVAF and the median number of GAs per ctDNA sample significantly increased at the time of PD vs. non-PD (12.31 vs. 2.10, p $<$ 0.0001, and 3 vs. 1, p = 0.0006, respectively). Delta ctDNA aVAF increases predicted radiologic PD with an area under the receiver operating characteristic curve of 0.84 (95%CI: 0.65-0.95, p $<$ 00.1). Delta ctDNA aVAF improved the patient risk stratification, pts with both decreased delta ctDNA aVAF and non-PD had the longest overall survival (Log-rank p = 0.05). A subgroup of 20 pts. had increasing ctDNA aVAF and $\geq$ 1 available subsequent radiologic scans within six months. Increasing ctDNA VAF $\geq$1 predicted PD in 90% (18/20) of pts with a median lead time of 92 days over imaging. APOBEC3-induced mutations (A3-m) were identified in ctDNA samples of (23%) 12/53 pts. Pts. with ctDNA A3-m had longer median PFS on immune checkpoint blockade than pts. without (17 vs. 3 months, Log-rank p = 0.01). There was no significant difference in OS according to ctDNA A3m status (Log-rank p = 0.37). Serial ctDNA provided insights into the clonal dynamics of treatment resistance, including the acquisition of *ERBB2* S653C resistance mutation at the time of PD on lapatinib. **Conclusions:** Serial ctDNA predicts clinical outcomes and provides real-time assessment of treatment effectiveness in pts. with advanced UC. This has the potential to guide future adaptive therapy paradigms. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

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Outcomes according to histological variants of urothelial carcinoma after neoadjuvant chemotherapy in the GETUG-AFU V05 VESPER trial.

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Background: The histological variants of urothelial carcinoma (UC) may impact the outcomes after neoadjuvant chemotherapy in muscle invasive bladder cancer (MIBC). Previous studies provided contradictory results because of bias related to their retrospective design. Our aim was to assess pathological response and 3-year (yr) progression free survival (PFS) according to UC variants for patients included within the French prospective Vesper clinical trial (NCT01812369). **Methods:** 493 patients received dose-dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin (dd-MVAC) or Gemcitabine and Cisplatin (GC) after randomization in the VESPER trial. This ancillary study was restricted to 437 patients treated in neoadjuvant setting. A central pathological review of initial transurethral diagnostic specimens allowed to assess UC variants (if $\geq$10% tumor area) and the presence of tumor emboli, perineural invasion, and CIS. **Results:** Slides were available for central review in 303 cases. UC variants were present in 180 patients (59%). Tumor emboli, perineural invasion, and CIS were noticed in 119 (39%), 24 (8%) and 143 (47%) cases. In comparison with pure UC, the presence of UC variants was not associated with different complete pathological response (ypT0N0) (OR 0.78, 95% CI 0.48-1.27) or 3 yr PFS (HR 1.25, 95%CI 0.83-1.86). Tumor emboli were negatively associated with ypT0N0 (OR 0.57, 95%CI 0.35-0.95, p = 0.029), organ confined disease (OR 0.44, 95%CI 0.26-0.75, p = 0.002) and 3 yr PFS (HR 1.81, 95%CI 1.23-2.67, p = 0.003). Perineural invasion were negatively associated with organ confined disease (OR 0.29, 95%CI 0.12-0.68, p = 0.005) and 3 yr PFS (HR 2.54, 95%CI 1.47-4.40, $p < 0.001$). There was no association for CIS. **Conclusions:** In the VESPER trial, UC variants were not associated with distinct pathological response or 3 yr PFS after neoadjuvant chemotherapy. Future studies will determine whether molecular subtypes are associated or not with distinct outcome. Research Sponsor: French Health Ministry (PHRC).

Association between CD47 expression and clinicopathologic characteristics and survival outcomes in MIBC.

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Background: CD47 is an antiphagocytic molecule that plays a critical role in immune surveillance. A variety of malignancies have been shown to evade the immune system by increasing the expression of CD47 on the cell surface. As a result, anti-CD47 therapy is under clinical investigation for these. CD47 overexpression is associated with negative clinical outcomes in lung and gastric cancers; however, the expression and functional significance of CD47 in bladder cancer is not fully understood. **Methods:** We retrospectively studied patients with muscle invasion bladder cancer (MIBC) on transurethral resection of bladder tumor (TURBT) who subsequently underwent radical cystectomy (RC) with or without neoadjuvant chemotherapy (NAC). CD47 expression was examined by immunohistochemistry in both TURBT and matched RC specimens. Expression levels ≥1% were considered positive. The difference between CD47 expression levels between TURBT and RC were also compared. The association of CD47 levels (TURBT) with clinicopathological parameters and survival outcomes were evaluated by Person's chi-squared test and Kaplan-Meier method respectively. **Results:** A total of 87 MIBC patients were included. The median age was 66 (39-84) years. The majority of patients were Caucasian (95%), male (79%), and age $>$ 60 (63%). Most patients (75%) underwent NAC prior to RC. Of those who received NAC, 35% were responders and 64% were non-responders. Responders includes those with a pathologic complete response (T0) or partial response (Tis or T1); non-responders included those with stage ≥ T2. The final reported stages for all patients were as follows: stage 0 (32%), stage I (1%), stage II (20%), stage III (43%), and stage IVA (5%). 60% of patients were alive, 40% died from bladder cancer, and 30% had disease recurrence at a median follow-up of 3.1 (0.2-14.2) years. CD47 levels were detectable in 38 (44%) TURBT samples. There was no association between CD47 levels and clinicopathological parameters such as age, gender, race, NAC, final stage, disease recurrence, and overall survival (OS). Patients $>$ 60 ($p = 0.006$), non-responders ($p = 0.002$), stage ≥ III ($p < 0.001$) were associated with worse OS by univariate analysis. There was no significance with multivariate analysis. There was a slight positive trend for decreased CD47 levels between TURBT and RC in patients who received NAC ($p = 0.5$), though this did not reach statistical significance. **Conclusions:** CD47 expression is not a prognostic marker for MIBC patients. However, expression of CD47 was detected in nearly half of MIBCs, and future studies are needed to explore a potential role for anti-CD47 therapy in these patients. Furthermore, there was a slight positive trend between decreased CD47 levels (from TURBT to RC) in patients receiving NAC. More research is needed to understand how NAC may or may not modify immune surveillance mechanisms in MIBC. Research Sponsor: None.

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Bacteria-specific CXCL13-producing follicular helper T cells are putative prognostic markers to neoadjuvant PD-1 blockade in muscle-invasive urothelial carcinoma.

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Background: Immune checkpoint inhibitors (ICIs), such as anti-PD-1/PD-L1 antibodies, have emerged as a successful immunotherapeutic strategy for advanced and metastatic urothelial cancer (UC). Therapeutic blockade of PD-1 or PD-L1 with monoclonal antibodies leads to durable tumor regressions in up to 25% metastatic muscle invasive UC (MIBC). Neoadjuvant use of ICI also showed remarkable efficacy and represents a unique opportunity to study immunodynamics during PD-1 blockade to decipher functional predictors of response and resistance. **Methods:** Patients diagnosed with T2-T4aN0M0 MIBC were treated with 3 cycles of neoadjuvant pembrolizumab before cystectomy in the PANDORE trial (NCT03212651). The primary endpoint was pathologic complete response (ypT0N0). Secondary endpoints focused on safety, progression-free survival (PFS) and biomarker analysis. We performed longitudinal analysis of peripheral and tumor infiltrating lymphocytes, tumor microbiome as well as soluble factors using high dimensionnal immune phenotyping by mass cytometry, immuno-fluorescence and -histochemistry and multiplex immunoassays. Humoral and cellular recall immune memory against urinary tract commensals were studied. **Results:** Thirty-nine patients were enrolled from October 2017 to December 2019. All but 5 (n = 34 patients (87.2%)) proceeded with cystectomy. Ten patients presented with ypT0N0 (29.4%; 95% CI: 15.1 %-47.5 %). Multidimensional biomarkers analysis showed that baseline follicular T helper (Tfh) and post-pembrolizumab tertiary lymphoid structure (TLS) and activated B cells were associated with outcome ($p = 0.005$, $p = 0.01$ and $p = 0.04$, respectively). Plasma CXCL13 (the prototypic chemokine secreted by Tfh and involved in TLS functions) increased after 1 cycle of PD-1 blockade in responders and patients without progression at 24 months ($p = 0.002$ and $p = 0.0001$, respectively). Focusing on MIBC tumor microbiome, we showed that intracellular Gram negative bacteria and other commensals were more frequent in tumoral than in normal urothelium ($p = 0.04$). Interestingly, basal CXCL13-secreting $CD4^+$ T cells and IgG directed against urinary pathobionts such as *Escherichia coli* predicted prolonged PFS ($p = 0.01$ and $p = 0.001$, respectively). **Conclusions:** Our results suggest that urothelial commensals could induce specific Tfh and B cell responses that were re-invigorated by PD-1 blockade and associated with clinical benefit to pembrolizumab. Further analyses are needed to validate the predictive value of commensal-specific Tfh in UC and other epithelial cancers that are directly or indirectly exposed to bacteria. Clinical trial information: NCT03212651. Research Sponsor: MSD.

SWOG S1314: A randomized phase II study of co-expression extrapolation (COXEN) with neoadjuvant chemotherapy for localized, muscle-invasive bladder cancer with overall survival follow up.

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Background: This trial evaluated COXEN, a gene expression model, as a predictive biomarker in muscle-invasive bladder cancer (BC) patients randomized to Gemcitabine-Cisplatin (GC) or dose-dense Methotrexate-Vinblastine-Adriamycin/doxorubicin-Cisplatin (ddMVAC). Primary results correlating COXEN with pathologic response at surgery have been reported. This secondary analysis includes progression-free (PFS) and overall survival (OS). **Methods:** Eligibility included Stage cT2-T4a N0 M0, urothelial BC (mixed histology allowed), ≥ 5 mm of viable tumor, cisplatin eligible, with plan for cystectomy. 237 patients were randomized between ddMVAC, given every 14 days for 4 cycles, and GC, given every 21 days for 4 cycles. Cox regression was used to evaluate COXEN score or treatment arm association with PFS and OS, adjusting for stratification factors (stage and PS). **Results:** 167 patients were included in the primary COXEN analysis all having either at least 3 cycles of chemo and surgery within 100 days of last chemo or having progressed while receiving chemo. The COXEN scores were not significantly prognostic for OS or PFS in their respective arms; the COXEN GC score was a significant predictor for OS in pooled arms. OS and PFS data are shown for both scores in the table. In the intent to treat analysis (n=227), there was no significant difference in OS or PFS for ddMVAC versus GC (for OS, HR =0.87, 95% CI 0.54-1.40), p = 0.57); for PFS (HR= 0.76 95% CI 0.58-1.01, p = 0.055). Association of path response with OS will be presented. **Conclusions:** The COXEN GC score may be prognostic of survival in those receiving platinum-based neoadjuvant treatment. The randomized, prospective design provides estimates of OS and PFS for GC and ddMVAC that appear comparable, but this phase II trial is underpowered for definitive comparisons. The prospective data and correlative samples from S1314 will allow for further assessment of COXEN and other RNA and DNA based predictive and prognostic biomarkers. Clinical trial information: NCT02177695. Research Sponsor: U.S. National Institutes of Health.

COXEN Score	Treatment Arm	Outcome	Sample Size	Hazard Ratio*	HR 95% CI*	2-sided p value *
GC-specific	GC	OS	82	0.33	0.10, 1.13	0.08
GC-specific	GC	PFS	82	0.45	0.17, 1.20	0.11
MVAC-specific	MVAC	OS	85	0.99	0.40, 2.45	0.98
MVAC-specific	MVAC	PFS	85	1.56	0.75, 3.27	0.23
GC-specific	Both	OS	167	0.45	0.20, 0.99	0.047
GC-specific	Both	PFS	167	0.77	0.42, 1.40	0.39

*Adjusted for two stratification factors – clinical stage at baseline (T2 vs T3, T4a), PS (0 vs 1). Funding: NIH/NCI grant U10CA180888, U10CA180819, U10CA180820, U10CA180821.

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Prognostic impact of fibroblast growth factor receptor (FGFR) genomic alterations and outcomes in patients with metastatic urothelial.

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Background: FGFR mutations/translocations are druggable targets in metastatic urothelial cancer (mUC). However, the prognostic effect of these genomic alterations (GA) and their role in the response to conventional therapy remain poorly characterized. **Methods:** We undertook an observational retrospective study in four Academic Hospitals in Madrid, Spain. Clinical and molecular information of patients diagnosed of Urothelial Cancer (UC) between January 2010 and December 2020 was systematically reviewed. The objective of this work was to compare the outcome of mUC patients with GA in the FGFR 2-3 genes versus wild type tumors. Analyses for detection of FGFR translocations and mutations using DNA isolated from formalin-fixed and paraffinized tumor tissue samples consisted of either next-generation sequencing (Foundation One test; n = 68) or qualitative real-time polymerase chain reaction–based assays (n = 9) with TFGFR or QIAGEN therascreen® tests that evaluated somatic mutations within the FGFR2-3 gene: R248C, S249C, G370C and Y373C and fusions: FGFR3-TACC3v3, FGFR3-TACC3v1 and FGFR3-BAIAP2L1, FGFR2-BICC1 and FGFR2-CASP7. Overall response rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) were determined and Cox-regression analysis were performed to assess the prognostic impact of these alterations. **Results:** We identified 201 patients diagnosed with UC. Genomic profiling was available in 77 mUC with 28 patients harboring any FGFR GA. Regarding ORR to first line a trend towards a better outcome was identified in FGFR GA (mutation/translocation/fusion) vs wild type cases (57,7% vs 45,5%, p=0,46). However, median OS was significantly worse among FGFR GA (mutation/translocation) vs FGFR wt tumours (13.8 vs 26.2 months, p=0,021). Prognostic factors associated with an unfavorable outcome in multivariable analysis were visceral metastases (HR 7,29 95% CI 1.6-32,3), ECOG >1 (HR 7,03 95% CI 2,59-19,1), first line treatment with checkpoint inhibitors (HR 2,67; 95% CI 1,06-6,74) and the presence of FGFR GAs (HR 2,98, 95% CI 1.37-6.5). **Conclusions:** Despite a better response to first line treatment, overall FGFR GA showed to be an independent risk factor in mUC. Thus, this determination should be included in new prognostic models. Research Sponsor: None.

Univariable and multivariable analysis for overall survival in the first line treatment setting for mUC.

		Univariable		Multivariable	
Variable	Modalidad	HR	95% CI	HR	95% CI
Age	(continuous)	1.02	0.989 - 1.06	1.03	1.00 - 1.07
Location	Non bladder	1 (ref)	-	1 (ref)	-
	Bladder	0.85	0.37 - 1.93	1.02	0.42 - 2.46
Treatment	Cisplatin	1 (ref)	-	1 (ref)	-
	Immunotherapy	1.26	0.57 - 2.77	2.67	1.06 - 6.74
	Other	1.87	0.92 - 3.83	3.55	1.56 - 8.11
Visceral metastases	No	1 (ref)	-	1 (ref)	-
	Yes	4.38	1.33 - 14.4	7.29	1.64 - 32.3
ECOG > 1	No	1 (ref)	-	1 (ref)	-
	Yes	2.89	1.34 - 6.25	7.03	2.59 - 19.1
FGFR	Wild-type	1 (ref)	-	1 (ref)	-
	Mutated	2.04	1.10 - 3.78	2.98	1.37 - 6.50

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Immune characterization of urothelial bladder carcinoma integrating transurethral resection of bladder tumor (TURBT) samples and serum: A feasibility study.

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Background: Urothelial bladder cancer (UBC) is characterized by high immunogenicity. Multiple immunotherapies both in the perioperative and advanced setting are being developed. However, we lack good predictive biomarkers of response to immunotherapy in UBC. We aimed to characterize the immune profile of UBC patients using TURBT and serum samples. **Methods:** 13 UBC biopsies from TURBT samples were analyzed along with sera of these patients. Biopsy samples were divided in two equal parts. One part was formalin-fixed paraffin embedded and stained for immune histochemistry [IHC] for the following markers (CD3, CD4, CD8, CD20, CD68 and PD-L1 using SP142 antibody) and results expressed in percentages. The other part was homogenized and processed for immune cell isolation (human tumor isolation Miltenyi Kit). Tumor cells were stained with PHK and double positive CD8 and PHK were isolated using a MACSTM procedure. Different immune cell populations were analyzed by flow cytometry for the following markers (CD3, CD4, CD8, CD20 and CD68) and results expressed in percentages. Cytokines were examined in sera using the Luminex multiparametric procedure and results were expressed as pg/mL. **Results:** IHC and flow cytometry data were comparable and identified three groups according to the immune cells associated with the tumors (Table). Groups 1 and 2 showed high and moderate levels of tumor activated $CD8^+$ T cells (1-4%) along with a higher expression of PD-L1 (40-20%). Group 3 lacked tumor activated $CD8^+$ T cells and show lower expression of PD-L1 (15%). All groups showed significant levels of Th2 cytokines (IL-4, IL-6 or IL-10) while very low or lack of Th1 cytokines (IFN or IL-2) was observed except in group 2. **Conclusions:** TURBT biopsies and serum analysis of cytokines could represent a valid approach to further evaluate potential predictive biomarkers of response to immunotherapy in UBC. Different immune populations subgroups were identified in our series and could potentially predict for diverse responses to treatment. Further prospective validation in larger series is ongoing to confirm these results. Research Sponsor: Astra Zeneca.

UBC tumor group	PD-L1	CD3	CD4	CD8	CD20	CD68	$CD8^+PHK^+$	IFN/IL-2	IL-4/IL-6/IL-10
1	40%	75%	20%	45%	20%	25%	2-4%	<0.1	>20/12.1/1.92
2	20%	60%	20%	40%	30%	20%	0.5-1%	6.4/1.29	13.7/4.9/6.9
3	15%	70%	40%	30%	50%	60%	0-0.2%	<0.1/1.2	<0.1/>20/1

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539 **Poster Session**

Development and clinical application of PredicineBEACON next-generation minimal residual disease assay for genitourinary cancers.

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Background: Tumor-informed minimal residual disease (MRD) assay has been studied in muscle invasive bladder cancer (MIBC) in IMvigor010 study. However, the current methods require the use of tumor tissue and lacking actionable insights. In this study, a tumor-agnostic and actionable MRD assay (PredicineBEACON) is developed with high sensitivity and capability to detect actionable mutations in blood- or urine-based circulating tumor DNA. **Methods:** PredicineBEACON tumor-agnostic MRD assay includes three components, i.e., baseline mutation identification, personalized panel design, and ultra-deep next generation sequencing of cancer variants. Step 1: whole exon sequencing with boosted depth in 600 cancer-related genes is performed using baseline tumor tissue or liquid biopsy (blood or urine) to identify somatic mutations. Step 2: Up to fifty somatic mutations are selected for personalized MRD panel design, in combination with the use of a fixed core panel of 500 actionable/hotspot variants. Step 3: MRD and actionable mutations were called from ultra-deep sequencing (100,000X). A companion low-pass whole-genome sequencing (LP-WGS) is performed to monitoring copy number variation (CNV). In the current study of patients with MIBC, urine samples at baseline were used for personalized variant generation. Urine samples under neoadjuvant immunotherapy and blood samples after radical cystectomy were collected and tested with the PredicineBEACON MRD assay. **Results:** PredicineBEACON MRD assay demonstrated a sensitivity of 0.005% tumor fraction. In patients of MIBC, urine-based MRD assay detected the dynamic changing of disease evolution under neoadjuvant therapy and preceded the radiographic response. Actionable mutations, including *FGFR3, TERT* and *PIK3CA* mutations, were detected. Copy number burden revealed by LP-WGS correlated with disease evolution. Plasma-based MRD assay on the patients after radical cystectomy is currently ongoing. **Conclusions:** PredicineBEACON tumor-agnostic MRD assay provides an ultra-sensitive and actionable MRD detection with high sensitivity and specificity. Assessment of MRD could potentially be leveraged, for example, to avoid overtreatment of early stage of genitourinary cancers such as non-metastatic prostate cancer, non-muscle invasive bladder cancer and muscle invasive bladder cancer. Research Sponsor: National Natural Science Foundation of China.

Association of TMB and PD-L1 with efficacy of first-line pembrolizumab (pembro) or pembro + chemotherapy (chemo) versus chemo in patients (pts) with advanced urothelial carcinoma (UC) from KEYNOTE-361.

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Background: The 3-arm, open-label, phase 3 KEYNOTE-361 study (NCT02853305) evaluated first-line pembro ± chemo vs chemo in advanced UC regardless of PD-L1 status. The trial did not meet its primary end points of superior PFS and OS with pembro + chemo vs chemo and thus analysis of pembro monotherapy (mono) vs chemo was exploratory. We explored the association of TMB status and PD-L1 combined positive score (CPS) with clinical outcomes in KEYNOTE-361. **Methods:** In pts with TMB and/or PD-L1 data, the association between TMB (via whole exome sequencing) and PD-L1 (via PD-L1 IHC 22C3 pharmDx) and clinical outcomes (ORR, PFS, and OS) was evaluated. In each treatment arm, the hypotheses regarding the associations were evaluated using logistic regression (ORR) and Cox proportional hazards regression (PFS; OS), and 1-sided (pembro; pembro + chemo) and 2-sided (chemo) *P* values were calculated; significance was prespecified at $\alpha = 0.05$ without multiplicity adjustment. Clinical utility was assessed using prespecified cutoffs of 175 mut/exome (TMB) and CPS 10 (PD-L1). Clinical data cutoff was April 29, 2020. **Results:** 820/993 pts (82.6%) had evaluable TMB data (pembro, 252; pembro + chemo, 282; chemo, 286). TMB ($\log_{10}$) was significantly positively associated with ORR, PFS, and OS for pembro ($P < 0.001$, < 0.001, and 0.007, respectively) and PFS and OS for pembro + chemo ($P = 0.007$ and 0.010, respectively). The area under the receiver operating characteristics (AUROC) curve (95% CI) for discriminating response was 0.64 (0.56-0.71) for pembro, 0.53 (0.46-0.60) for pembro + chemo, and 0.52 (0.45-0.59) for chemo. Efficacy by TMB cutoff is reported in the Table. All 993 pts had PD-L1 data (pembro, 302; pembro + chemo, 349; chemo, 342). PD-L1 was significantly positively associated with PFS for pembro ($P = 0.006$) and ORR for pembro + chemo ($P = 0.042$) but not chemo. Efficacy by PD-L1 CPS is reported in the Table. **Conclusions:** Strong associations were observed between TMB and all 3 clinical outcomes (ORR, PFS, and OS) with pembro mono in the first-line setting and a reduced association was observed between TMB and clinical outcomes with pembro + chemo. No consistent associations were observed between PD-L1 and clinical outcomes with pembro mono or pembro + chemo. Clinical trial information: NCT02853305. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	TMB ≥175	TMB ≥175	TMB < 175	TMB < 175
	P (n = 78) vs C (n = 85)	P+C (n = 86) vs C (n = 85)	P (n = 74)vs C (n = 201)	P+C (n = 196) vs C (n = 201)
PFS, HR (95% CI)	0.81 (0.54-1.21)	0.70(0.48-1.02)	1.37 (1.09-1.74)	0.80(0.63-1.00)
OS, HR (95% CI)	0.69 (0.45-1.04)	0.77(0.53-1.14)	0.92(0.73-1.16)	0.79(0.63-0.99)
	CPS ≥10	CPS ≥10	CPS < 10	CPS < 10
	P (n = 156) vs C (n = 153)	P+C (n = 158) vs C (n = 153)	P (n = 146) vs C (n = 189)	P+C (n = 191) vs C (n = 189)
PFS, HR (95% CI)	1.32 (1.01-1.74)	0.76(0.58-1.01)	1.28 (1.00-1.65)	0.76(0.60-0.97)
OS, HR (95% CI)	1.03 (0.78-1.35)	0.83(0.62-1.09)	0.83(0.64-1.07)	0.82(0.65-1.03)

HRs adjusted for ECOG PS.

541 **Poster Session**

Characterization and functional analysis of microbiome in bladder cancer.

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Background: The role of microbiome in genitourinary cancer is an emerging field, with evidence implicating the important role of microbiome as causative factors or cofactors in tumorigenesis and drug metabolism. Our study aims to characterize healthy and bladder cancer enterotypes in the gut and identify functional alterations through the use of metagenomics data. **Methods:** After prospective collection of 29 rectal swab samples of bladder cancer (BCa) patients undergoing cystectomy, and 32 healthy volunteers, we perform 16S rRNA amplicon sequencing on 61 samples (29 with bladder cancer, 32 without cancer). Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) was applied to infer functional categories associated with taxonomic composition. The p values were adjusted using the false discovery rate. The a- and b-diversity analyses were performed using QIIME. The Mann-Whitney U test was employed to evaluate the statistical significance of b-diversity distances within and between groups of interest. **Results:** Across all the bladder cancer stool samples, estimation of relative abundance revealed of the five most dominant bacterial populations was Bacteroidales (46.21%), Clostridiales (32.29%), Burkholderiales (9.07%), Erysipelotrichales (3.20%) and Lactobacillales (2.20%). In contrast, healthy controls exhibited an increased relative abundance of Enterobacteriales (10.75% vs 0.52%) and Pseudomonadales (8.33% vs 0.18%) as compared to tumor samples. The microbial diversity differences between Bca and normal samples showed no differences across alpha diversity metrics (Shannon diversity $p>0.05$) as compared to normal tissue. However, there was significant difference in clustering of organisms as determined by principal coordinate analysis (PCoA) ordination of unweighted UniFrac Distances, ($p = 0.002$). Furthermore, upon stratification of patients on smoking status (all healthy=nonsmokers), clustering persisted, albeit non smokers with bladder cancer displayed an intermediate across PCoA. Bca samples exhibited higher LDA score *Campylobacterales* (log change 8.0, $p<0.001$, $p_{adj} <0.001$),*Fusobacteriales* (log change 6.11, $p<0.001$/ $p_{adj}<0.01$), *Epysipelotrichales (*log 2.55, $p<0.001/p_{adj} <0.001$*), Actinomycetales* (log change 1.86, $p=0.001$/ $p_{adj}<0.001$), *Verrucomicrobiales (*log change 1.78, $p=0.017/p_{adj}=0.031$) and *Enterobacteriales* (log change -1.54, $p = 0.017$/ $p_{adj} = 0.132$). **Conclusions:** In conclusion, our study provides preliminary evidence that the GI microbiota is different in bladder cancer patients. Collectively, our study highlights distinct microbial overexpression of Campylobacter and Fusobacterium in Bca cohort not previously reported, both implicated in tumorigenesis, and could serve as a target that could be modulated to enhance treatment response. Research Sponsor: Case Comprehensive Cancer Center Microbiome Grant.

Characterization of fungal mycobiome in bladder cancer.

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Background: Bacterial dysbiosis accompanies carcinogenesis in malignancies such as colon, breast and pancreatic cancer. However, the role of fungal mycobiome has not been evaluated in bladder cancer. With the sexual dimorphism that exists within bladder cancer (Bca) prevalence and survival, our study aims to characterize fungal mycobiome composition in Bca. **Methods:** This is a single site, non-randomized, prospective study of patients with the diagnosis of muscle invasive bladder cancer (MIBC) undergoing cystectomy from September 2020 to May 2021. Stool samples were collected during surgery using aseptic technique. We utilized the ITS1 region from DNA sample extracts, which was amplified in triplicate using primers with high specificity for ascomycete fungi (fluorescently-labeled forward primer ITS1F (CTTGGTCATTTAGAGGAAGTAA) and unlabeled reverse primer ITS2 (GCTGCGTTCTTCATCGATGC). Fungal PCR products were separated on the SCE 9610 capillary DNA sequencer (Spectrumedix LLC, State College, PA) using GenoSpectrum software to convert fluorescent output into electropherograms. Hierarchical clustering by Bray-Curtis distance was performed using *hclust2*. Mean normalized abundance for each amplicon was calculated from the three PCR replicates of each sample, excluding means below 1%. **Results:** A total of 29 patients (17 males and 12 females) were enrolled. The median (IQR) age was 74 yo (63-77), males, and 68.5 yo (58-78), females. Per figure 1, *Saccharomycecales* dominated the fungal community at order level with mean relative abundance of 36.35% females, and 21.20%, males. (Figure 1D) *Tremellales* was the second most notable order, composing 8.22% and 5.13% of male and female samples. There were no differences seen in alpha and beta diversity (Figure 1C) (Figure 1A, C), notable differences were seen across orders. The greatest difference between sexes in LDA(M:F) were noted in *Saccharomycecales* (log change -4.686, p=0.001/ p_{adj}= 0.01), *Tremellales* (log change 5.119, p=0.001/p_{adj}= 0.01), and *Sporidiobolales* (log change 4.839, p=0.001 p_{adj}= 0.03). (Figure 1B). Female bladder cancer patients demonstrating an increase abundance of *Saccharomycecale.* When assessing differences in fungal composition in patients with history of neoadjuvant therapy(NAC) (receipt vs none), patients with history of NAC exhibited a 3.48 increase in *Saccharomycecale (*p_{adj}= 0.015 *),* 4.81 increase *Tremalles (*p_{adj}= 0.009) and 4.37 increase *Pleosporales(*p_{adj}= 0.009). **Conclusions:** Mycobiome is an integral part of gut microbiota, with fungal elements relatively poorly studied. Nevertheless, the association between fungal dysbiosis and carcinogenesis across multiple cancers exists. Our study is the first to characterize fungal profile in bladder cancer patients, stratified by sex and receipt of NAC, with results highlighting key fungal players: *Saccharomycecale, Tremallales, Pleosoporales.* Research Sponsor: Case Comprehensive Cancer Center Microbiome Grant.

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Novel use of ctDNA to identify locally advanced and metastatic upper tract urothelial carcinoma.

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Background: Upper tract urothelial carcinoma (UTUC) is an aggressive cancer for which use of neoadjuvant chemotherapy (NAC) is limited by suboptimal clinical staging prior to nephroureterectomy. Detection of circulating tumor DNA (ctDNA) is associated with locally advanced and metastatic urothelial carcinoma of the bladder and may help identify UTUC patients who would benefit from NAC. Here we examine the feasibility and utility of plasma ctDNA in the diagnosis of non-organ confined high-risk UTUC. **Methods:** Patients with high-grade cTa-T2 UTUC without radiographic evidence of metastatic disease undergoing up-front radical nephroureterectomy (RNU) were prospectively accrued. Blood was collected preoperatively on the day of surgery, and plasma and buffy coat were processed for extraction of ctDNA. FFPE samples from RNU were used for tissue genomic DNA extraction. Next-generation sequencing (NGS) was used for variant profiling. Plasma and somatic tissue mutations were called by comparing with matched buffy coat samples. Detection of cancer variants with a mutation allele frequency (MAF) $\geq$ 0.25% and hotspot variants with a MAF down to 0.1% were reported for plasma samples targeted by a NGS panel (PredicineCARE). Variants with a MAF $\geq$ 5% and hotspot variants with a MAF down to 2% were reported for FFPE samples. **Results:** NGS analyses of matched FFPE and plasma samples were successfully performed for all 15 accrued UTUC patients. Alterations in MYC amplification (62%), TERT promoter (62%), TP53 (38%), FGFR3 (31%), ERBB2 (25%), ARID1A (19%), and PIK3CA (19%) were demonstrated in urothelial tumor tissue. Matched plasma ctDNA showed prevalent alterations in the TERT promoter (47%), TP53 (30%), ARID1A (20%), ERBB2 (20%), FGFR3 (20%), and PIK3CA (17%). Five patients (33%) had detectable plasma ctDNA mutations concordant with tumor-based genotypes using the targeted NGS panel. All patients with detectable preoperative ctDNA had advanced staging ($\geq$pT2 or $\geq$pN1) and lymphovascular invasion on final pathology, resulting in a 71.4% sensitivity. The panel was 100% specific with no patients with pTis, pTa, or pT1 and pN0 having detectable concordant ctDNA mutations. **Conclusions:** Prospective ctDNA analysis using a targeted NGS panel is a feasible nonsurgical approach to prediction of high-risk UTUC and has the potential for identification of upper tract urothelial cancer patients that may benefit from NAC. Research Sponsor: Predicine Inc., Junior Scientist Research Partnership Award, H Lee Moffitt Cancer Center & Research Institute.

Clinical outcomes in advanced urothelial cancer (UC) patients who experienced immune-related adverse events (irAEs) after immune checkpoint inhibitor monotherapy (ICI).

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Background: Immune checkpoint inhibitors (ICIs) continue to demonstrate promise in treatment of advanced urothelial carcinoma (UC). Some patients undergoing ICIs experience immune related adverse events (irAEs) and may serve as a marker of response. We investigated the relationship between irAEs and clinical outcomes in UC patients treated with ICIs. **Methods:** A retrospective study of 70 UC patients treated with ICI monotherapies at Winship Cancer Institute from 2015-2020 was done. Overall survival (OS) and progression-free survival (PFS), defined as time from ICI initiation to death and clinical or radiographic progression, respectively as well as clinical benefit (CB), defined as best radiographic response of complete response, partial response, or stable disease for $\geq$ 6 months per RECIST v1.1, were used to measure clinical outcomes. Cox proportional hazards and multivariable analyses (MVA) were used to model associations with OS and PFS. **Results:** Most patients were male (70%) with a median age of 68.7 years (28.0-91.0). Most patients (95%) had urothelial carcinoma and most (81%) received at least 1 prior treatment. One third of patients had ECOG PS greater than or equal to 2. Of patients that experienced an irAE (35%), the most common were dermatologic (12.9%) and arthralgia (0.5%). In addition to significantly longer treatment duration, irAE patients had significantly increased OS (HR:0.38, 95% CI:0.18-0.79, p=0.009), significantly longer PFS (HR:0.27, 95% CI:0.14-0.53, $p < 0.001$), and significantly greater CB (OR:4.20, 95% CI:1.35-13.06, p=0.013). Patients who experienced dermatologic irAEs had significantly increased OS, PFS, and CB (Table). **Conclusions:** Our results demonstrate that UC patients undergoing ICI therapy who experience irAEs, especially dermatologic irAEs, had improved clinical outcomes. This suggests that irAEs may serve as a clinical biomarker of advantageous response in patients receiving ICI. Future prospective studies are needed for validation. Research Sponsor: None.

MVA* of association between irAEs and clinical outcomes in UC patients.

	Total weeks on treatment		OS		PFS		CB	
Variable	**B**	**p-value**	**HR (CI)**	**p-value**	**HR (CI)**	**p-value**	**OR (CI)**	**p-value**
irAE (n=25)	24.74 (9.67-39.81)	**0.002****	0.38 (0.18-0.79)	**0.009****	0.27 (0.14-0.53)	**<0.001****	4.2 (1.35-13.06)	**0.013****
			Median OS(CI): NR (9.9, NR)		Median PFS (CI): 8.5 (3.3, NR)		CB rate: 52%	
No irAE (n=45)	1		1		1		1	
			Median OS (CI): 7.1 (2.4, 11.7)		Median PFS (CI): 2.2 (1.7, 3.2)		CB rate: 23%	
Derm. irAE (n= 9)	34.12 (12.42-55.82)	**0.003****	0.23(0.07-0.78)	**0.019****	0.18 (0.06-0.53)	**0.002****	7.68 (1.51-38.93)	**0.014****
			Median OS (CI): NR (5.5, NR)		Median PFS (CI): 33.3 (2.8, NR)		CB rate: 67%	
No derm. irAE (n=61)	1		1		1		1	
			Median OS(CI): 9.2 (5.8, 12.4)		Median PFS (CI) 2.6 (2.2, 3.8)		CB rate: 29%	

*MVA were build using the backward selection method at alpha level of 0.1. **Statistical significance at alpha < 0.05.

545 **Poster Session**

PD-L1 expression and BCG response in nonmuscle invasive bladder cancer.

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Background: Intravesical bacillus Calmette Guerin (BCG) is the standard of care adjuvant therapy for high risk non-muscle invasive bladder cancer (NMIBC), yet many patients experience recurrence or disease progression. The mechanism of action of BCG is believed to be related to stimulation of immune surveillance. Relatedly, systemic immune checkpoint inhibition is currently being utilized in advanced bladder cancer and approved for BCG unresponsive NMIBC. We sought to determine the association between PD-L1 expression and BCG treatment. **Methods:** We identified 102 BCG-naïve patients with high grade (HG) NMIBC treated with BCG. All patients underwent initial transurethral resection (TUR) for pathologic diagnosis. Dako 22c3 assay was used to determine PD-L1 expression. Patients were defined as PD-L1 positive if the combined positive score (CPS) $>$ 0. BCG unresponsiveness was defined by presence of high grade disease at 6 months following adequate BCG (one induction and maintenance cycle or two induction cycles) for pT1 or 12 months for CIS or presence of pT1 at 3 months following induction. HG relapse was defined as presence of any HG disease after being followed for 6 months after BCG. **Results:** The median follow-up time was 57 months. Median number of BCG maintenance cycles was 1, and 17 (16.7%) patients underwent immediate reinduction BCG. PD-L1 expression was observed 5.9% of pTa, 30.0% of pT1, and 3.6% of CIS. BCG unresponsiveness and HG relapse were observed in 32 (35.6%) and 29 (34.5%) patients, respectively. On univariate analysis, PD-L1 expression was inversely associated with BCG unresponsiveness (OR = 0.112; 95% CI 0.014-0.898) but not high grade relapse (OR = 0.296; 95% CI 0.061-1.440). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PD-L1 expression for BCG responsiveness were 22%, 97%, 93%, and 41%, respectively. The post-test probability of BCG responsiveness was 93% in patients positive for PD-L1 based on a positive likelihood ratio of 7.33 for PD-L1 expression. On multivariate regression, pT1 (OR = 0.159; 95% CI 0.045-0.600), CIS (OR = 0.247; 95% CI 0.071-0.857), and PD-L1 expression (OR = 15.625; 95% CI 1.779-142.857) were independently associated with BCG responsiveness. **Conclusions:** PD-L1 expression in HG NMIBC was low, and patients with PD-L1 expression at initial TUR were more likely to harbor invasive disease. Patients showing PD-L1 expression were more likely to demonstrate BCG responsiveness. These findings suggest a role of PD-L1 in the immune surveillance mechanism of BCG at initial pathologic diagnosis and may assist in predicting responses to BCG among patients with HG NMIBC. Further investigation is required to determine if additional immune checkpoint markers have strong correlation with BCG response, particularly among patients without PD-L1 expression. Research Sponsor: None.

546 **Poster Session**

Comprehensive molecular characterization of muscle-invasive bladder cancer (MIBC) treated with durvalumab plus olaparib in the neoadjuvant setting: Neodurvarib trial.

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Background: Immune checkpoint inhibitors have been incorporated to early-stage bladder carcinoma treatment recently. Durvalumab is a PD-L1 blocking antibody active in advance urothelial tumors and under evaluation in other settings of the disease. PARP inhibitors have shown activity in a variety of tumors with Homologous Recombination Deficiencies (HRD). The combination of Durvalumab plus Olaparib could present a synergistic effect, but its efficacy and potential biomarkers are under exploration. NEODURVARIB is a phase II clinical trial assessing the combination of Durvalumab plus Olaparib in MIBC (NCT03534492; SOGUG-2017-AIEC(VEJ)-2). Clinical activity and safety have been previously communicated by our group. Here we present the basal molecular profiles and their evolution under treatment with this combination. **Methods:** cT2-T4a MIBC aimed for cystectomy were treated during 6-8 weeks precystectomy. Pre- and post-treatment tumor and blood samples from 26 patients were collected. Pattern of immune infiltration was determined by IHQ. Genomics (mutational pattern, HRD and Tumor Mutation Burden [TMB]) and transcriptomics (differentially expressed *loci,* functional enrichment, molecular clustering and MIBC molecular subtyping) analysis were performed. Circulating immune populations were assessed using flow cytometry. **Results:** In basal (TURBT) samples, the frequency of mutations in genes commonly altered in MIBC (*TP53*, *MLL2, ARID1A, FGFR3,* among others), HRD and TMB were similar to previous reports in MIBC and did not differ between responders and non-responders. Additionally, mutational patterns remained stable between baseline (TURBT) and post-treatment (cystectomy) samples. Regarding transcriptomics, GSEA showed enrichment of Epithelial Mesenchymal Transition (EMT), TGFβ and inflammatory/infection related classes in resistant tumors. Interestingly, differentially expressed genes in responders vs. non-responders were significantly regulated by epigenetic factors (EZH2/Suz12/PRC2 network). Transcriptomic-based estimations of the stromal/immune infiltration and MIBC molecular subtyping also showed a switch of the tumor microenvironment due to the treatment (luminal to basal/squamous transitions), reinforced by significant changes in the expression of immune markers (higher PDL1 and FAP scores in cystectomies). Lastly, circulating senescent T-cells were correlated with pathological complete response. **Conclusions:** Genetic alterations remained unchanged in bladder cancers treated with Durvalumab plus Olaparib. However, an enrichment of EMT signatures and a switch towards basal/squamous phenotypes were observed in resistant tumors. These findings underscore the relevance of modifications in gene expression as potential mechanisms of resistance to this combination. Clinical trial information: NCT03534492. Research Sponsor: Astra Zeneca Pharmaceuticals.

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Tumor mutational burden as a predictive biomarker for immune checkpoint inhibitor versus chemotherapy benefit in first-line metastatic urothelial carcinoma: A real-world study.

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Background: There is an unmet need to identify metastatic urothelial carcinoma (mUC) patients who might be spared chemotherapy in 1st line. Anti-PD-(L)1 immune checkpoint inhibitors (ICPI) alone without chemotherapy did not show superiority to platinum-based chemotherapy in ITT populations of DANUBE, KEYNOTE-361, and IMvigor130. However, DANUBE and IMvigor130 reported secondary subgroup analyses, both suggesting enhanced benefit for ICPI vs. chemotherapy in patients with tumor mutational burden (TMB) $\geq$ 10 (mutations/megabase), using same cutoff and assay as pan-tumor CDx for pembrolizumab approved in later lines of therapy. We sought to determine if TMB $\geq$ 10 identified a group of enhanced relative ICPI benefit (single-agent anti-PD[L]1 w/o chemo) in real-world settings where patients are less eligible for chemotherapy. **Methods:** Association of genomic data with clinical variables and outcomes in cohort of patients with mUC treated January 2011- April 2021. Longitudinal de-identified clinical data from approximately 280 U.S. academic or community-based cancer clinics were derived from electronic health records, curated via technology-enabled abstraction by Flatiron Health and linked to genomic testing by Foundation Medicine. 849 1st line mUC patients received either ICPI (n = 307) or chemotherapy (n = 542) at physician's discretion in standard of care settings. All patients underwent genomic testing using Foundation Medicine comprehensive genomic profiling assays (FoundationOne© or FoundationOne©CDx). PFS and OS were assessed unadjusted and adjusted for imbalances using propensity scores. **Results:** 273 of 849 (32.2%) patients had TMB $\geq$ 10. Pre-therapy characteristics: patients assigned ICPI vs. chemotherapy had comparable TMB, primary disease site, histology, smoking status, and PD-L1 staining, but were generally older (median years: 72 vs. 67, $p < 0.001$), higher ECOG scores ($p < 0.001$), lower CrCl (median ml/min: 49.8 vs. 59.7, $p < 0.001$), and lower hemoglobin (median: 11.5 vs. 12.1, $p < 0.001$). Unadjusted, TMB $\geq$ 10 group showed more favorable PFS (HR: 0.72, 95%CI: 0.52 – 0.99, p = 0.041) and OS (HR: 0.70, 95%CI: 0.49 – 0.1, p = 0.048) for ICPI vs. chemotherapy despite imbalances favoring outcomes on chemotherapy. ICPI vs. chemotherapy outcomes adjusted for imbalances: TMB $\geq$ 10 group showed more favorable PFS (HR: 0.65, 95%CI: 0.45 – 0.95, p = 0.026) and OS (HR: 0.61, 95%CI: 0.39 – 0.93, p = 0.022), while TMB $<$ 10 had comparable or worse PFS (HR: 1.30, 95%CI: 0.98 – 1.72, p = 0.06) and OS (HR: 1.03; 95%CI: 0.78– 1.34, p = 0.85). **Conclusions:** In real-world settings, 1st line mUC patients with TMB $\geq$ 10 have more favorable PFS and OS on single agent ICPI than chemotherapy, adding clinical validity to TMB as a predictive biomarker in patient populations less eligible for chemotherapy than reported trials. Research Sponsor: Foundation Medicine.

Clinico-genomic characterization of patients with metastatic urothelial carcinoma in real-world practice and development of a novel bladder immune prognostic index (BIPI).

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Background: Real-world data (RWD) linking clinical outcomes with comprehensive genomic profiling (CGP) may enable identification of biomarkers to guide treatment selection and stratification in future trials. The primary objective was to characterize patients with metastatic urothelial carcinoma (mUC) included in a clinic-genomic database (CGDB), comprised of the electronic health record-derived Flatiron Health database with linked FoundationOne CGP results. As secondary objective, a novel Bladder Immune Prognostic Index (BIPI) was developed. **Methods:** A retrospective exploratory analysis was performed of de-identified RWD, retrieved from the CGDB. Data from mUC patients starting first-line single-agent immune checkpoint inhibitors (ICIs) and an unmatched group treated with front-line platinum-based chemotherapy (CHT) between Jan 1, 2011, and Sept 30, 2019, were analyzed and correlated with overall survival (OS). Known driver alterations, tumor mutational burden (TMB), and PD-L1 expression were described. A BIPI predicting outcome with ICIs was developed using a Cox-LASSO model and validated externally in a phase II trial (NCT02951767). **Results:** Of the 1021 patients with mUC identified in CGDB, 118 ICI-treated and 268 CHT-treated patients were included. Median follow-up duration was 9.4 and 14.5 months, respectively. Median OS was 5.4 months (95%CI, 3.3–9.2) with ICIs and 8.2 months (95%CI, 6.8–10.0) with CHT. In ICI-treated patients, low albumin and metastatic disease at initial presentation were associated with worse OS [HR (95%CI) 2.15 (1.18–3.90), p =.012; 2.58 (1.30–5.10), p =.007, respectively] whereas surgery for organ-confined disease and high TMB (≥10 mut/Mb) were associated with improved OS (HR (95%CI) 0.56 (0.36–0.88), p =.012; 0.58 [0.35–0.95]; *p*=.03), respectively. In CHT-treated patients, those with high APOBEC had worse OS (HR 1.43 [95% CI, 1.06–1.94]; *p*=.02). Neither PD-L1 (HR 0.96 [0.37-2.46]; p =.93), *FGFR3* mutations (HR 0.98 [0.65-1.47]; p =.92) nor DNA damage-repair pathway alterations (HR 1.06 [0.73-1.52]; p =.77) were associated with OS. A novel BIPI for ICI-treated patients combining clinical and genomic variables (non-metastatic at initial diagnosis, normal albumin level, previous surgery for organ-confined disease, high TMB) was developed. Patients were categorized in 3 groups (low, intermediate, high risk) which correlated with OS. Median OS (95%CI) for low, intermediate and high risk was 11.7 (8.9−17.7), 4.1 (2.5–NE) and 2.4 months (1.0–4.0), (p <.001). Same results were observed in the validation cohort from an independent phase II immunotherapy trial in mUC (p <.001). **Conclusions:** This is the first time RWD including CGP were used to develop and validate a novel BIPI in mUC. This prognostic index may help patient selection in everyday practice and inform future trial design. Research Sponsor: None.

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FOXP3+ T-cell infiltration is associated with improved outcomes in metastatic urothelial carcinoma (mUC) treated with immune-checkpoint inhibitors (ICI).

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Background: Given that ICIs benefit a minority of mUC patients and are associated with significant costs, biomarkers are necessary to optimally utilize them in the clinic. Although FOXP3+ T-cells have been associated with an immune-cold environment in many cancers, studies in urothelial carcinoma have shown an opposite trend. **Methods:** Formalin-fixed paraffin-embedded slides from tumor specimens were collected for patients with mUC treated with ICI at Dana-Farber Cancer Institute. A novel multiplex immunofluorescence (mIF) panel, ImmunoProfile, was performed for PD-L1, PD-1, FOXP3, CD8 and DAPI, then scanned by a Vectra Polaris platform. Regions of interest were defined and used for quantitative analysis using PerkinElmer/Akoya. Intratumoral (IT) and tumor-stroma interface (TSI) density (cells/mm^2) of each cell type was calculated. Clinical data was collected through chart review, and associations between cell density and response were assessed. Wilcoxon Rank-Sum test between responders (CR/PR) and non-responders (SD/PD) was used to generate p-values, followed by Benjamini-Hochberg correction. Receiver-operating curve (ROC) and area-under-curve (AUC) calculations were performed to determine the optimal cutoff (OC) differentiating responders from non-responders. Cox proportional hazards models were used to estimate OS and PFS, accounting for type of therapy (single vs. combination ICI), baseline neutrophil-to-lymphocyte ratio (NLR), PD-L1 CPS, prior therapy, non-urothelial component, ECOG-PS and liver metastases (mets). **Results:** Of 35 patients assessed by ImmunoProfile, 32 were evaluable for response. Most patients (88%) were male and the median age at ICI start was 73 years. Median number of prior lines of therapy was 1 (range 0 – 3), and the majority (72%) was treated with single-agent ICI. Eight patients (25%) had CR/PR, eight had SD and 16 had PD as best response. Of all IF stains assessed, IT-TSI FOXP3 was the strongest predictor of objective response (q-value = 0.006), followed by IT-CD8 (q = 0.014). ROC analysis yielded an AUC of 0.812 (0.656 – 0.969) and the optimal cutpoint was set at 75 IT-TSI-FOXP3 cells/mm^2. ORR was 46% in FOXP3-high ($>$ 75/mm^2) vs 14% in FOXP3-low mUCs. A combined model using IT-TSI-FOXP3 and clinical covariates (NLR, ECOG-PS, line of therapy, histology, and liver mets) had an AUC of 0.929. PFS was significantly longer in the FOXP3-high group (7.9 [5.7 – NR] months) compared to the FOXP3-low group (2.3 [2.1 – 6.1] months) on multivariable analysis (p = 0.007). OS also showed the same trend (p = 0.1). **Conclusions:** In this pilot study of ImmunoProfile, a novel mIF panel, higher FOXP3+ infiltration in tumors was associated with better outcomes and a composite clinico-IHC panel exhibited robust prognostic impact in mUC pts treated with ICI. Further study of this mIF panel is warranted to implement it in routine practice. Research Sponsor: None.

Expanding the use of targeted therapy for urothelial bladder cancer (UBC): Non-*FGFR3* receptor tyrosine kinase (RTK) gene rearrangements (ReAr) and fusions (fus).

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Background: After the regulatory approval of erdafitinib targeting *FGFR* genomic alterations (GA), molecular profiling and targeted therapy indications may further expand in UBC. We queried a large database of advanced UBC to study the landscape of RTK ReAr and Fus to categorize additional targets beyond *FGFR1-3* that have potential to further personalize treatment of this disease. **Methods:** We analyzed data from 8,233 UBC cases, which underwent hybrid capture-based comprehensive genomic profiling (CGP). Tumor mutational burden (TMB) was determined on up to 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci. PD-L1 expression in tumor cells was assessed by IHC (Dako 22C3). **Results:** A total of 1,210 (14.7%) UBC featured known and likely large-scale (LS) internal ReAr with 414 (5%) ReAr in RTK genes. The ReAr/fus were distributed among *ABL1* (3), *ALK* (3), *BRAF* (29), *CDK12* (44), *CDK8* (1), *EGFR* (10*), ERBB2* (3), *FGFR1* (2), *FGFR2* (16*), FGFR3* (231), *FLT3* (1), *MAO2K4* (4), *NTRK1* (7*), NTRK2* (5), *NTRK3* (7), *RAF1* (31*), RET* (8) and *ROS1* (9). LS ReAr were divided into LS ReAr-associated gene deletions (1%), truncations (1%), rearrangements (61%) and fusions (37%). *FGFR3* fus accounted for 81% of RTK fus with *BRAF* and *RAF1* both at 2%. The greatest frequencies of kinase ReAr were in *CDK12* (29%), *FGFR3* (16%), *RAF1* (13%) and *BRAF* (12%). Additional noteworthy 'targetable' RTK ReAR and fus included *NTRK1-3* (19 cases), *ROS1* (9 cases), *RET* (8 cases) and *ALK* (1 case). 407 (98.4%) of the RTK ReAr/fus-positive UBC had only 1 RTK ReAr/fus GA and 7 (1.6%) had 2 ReAr ReAr/fus, 6 (85.7%) of which involved *FGFR3*. Compared with LS ReAR negative UBC, the LS ReAR UBC cases revealed similar gender and age characteristics, MSI status, similar frequencies of TMB ≥ 10 mut/Mb and PD-L1 expression in tumor cells ≥1% and ≥50%. **Conclusions:** At a 5% frequency, potentially 'targetable' RTK gene rearrangements and fusions are a rare but important opportunity to further personalize treatment selection of UBC, including RTK inhibitors, PARP inhibitors (*CDK12*) and immunotherapy. This potential for clinical trials supports broader CGP, compared to targeted *FGFR* sequencing, in order to uncover additional opportunities for precision therapies that have the potential to improve patient outcomes. Research Sponsor: Foundation Medicine Inc.

RTK Gene LS ReAr	Deletions	Duplications	Fusions	Rearrangements
ALK	2	0	0	1
BRAF	1	1	10	17
CDK12	0	0	0	44
FGFR3	0	0	207	24
NTRK1,2,3	0,0,0	0,0,0	2,1,2	5,4,5
RAF1	0	0	11	20
RET	0	0	3	5
ROS1	0	0	1	8

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Genomic sequencing for bladder urothelial carcinoma and its clinical implications for immunotherapy.

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Background: To explore the genomic and transcriptomic landscape of bladder cancer (BC) and its implication for treatment with an immune checkpoint inhibitor (ICI). **Methods:** We analyzed whole-exome and -transcriptome sequences of tumor samples from 64 BC patients who underwent surgical resection with either transurethral resection or radical cystectomy. For exploratory purposes, PD-L1 expression was evaluated in a subset of patients (n = 57) including those treated with ICI (n = 8). **Results:** We identified frequent molecular dysregulations in chromatin regulatory genes (*KDM6A*, *ARID1A*, *MLL2*, and *STAG2*) and recurrent copy number alterations. Thirty-five samples (54.7%) were PD-L1-positive (PD-L1 combined positive score $\geq$ 1) with a significantly higher exonic tumor mutational burden (TMB) compared to PD-L1-negative BC samples (P= 0.010). We observed that various immune-responsive pathways, including the PD-L1 signaling pathway, were enriched significantly in PD-L1-positive BCs. Interestingly, genes in the CTLA4 pathway were enriched significantly in PD-L1-positive BC as well. Among 8 patients who received ICI, progressive disease was confirmed in one patient, whose tumor had low exonic TMB, negative PD-L1 status, and a relatively colder microenvironment. **Conclusions:** Gaining new insights into the molecular landscape of BC will improve treatment strategies. Our analysis suggests a rationale for studying dual checkpoint inhibition against BC. Research Sponsor: Samsung Medical Center Research Fund., Korean Health Technology R&D Project through the Korea Health Industry Development Institute, and the Ministry of Health and Welfare.

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Longitudinal personalized urinary tumor DNA analysis in muscle-invasive bladder cancer from the neoadjuvant immunotherapy trial RJBLC-I2N003.

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Background: RJBLC-I2N003 is an investigator-initiated study to evaluate the clinical activity and predictive biomarkers for neoadjuvant immunotherapy with toripalimab (anti-PD-1) in muscle invasive bladder cancer (MIBC). **Methods:** Twenty patients with pathologically confirmed MIBC were enrolled and received toripalimab (3 mg/kg Q2W, 4 cycles) before radical cystectomy. The safety and efficacy of neoadjuvant toripalimab were assessed. Serial urinary cell-free DNA (ucfDNA) and blood cell-free DNA (bcfDNA) were obtained at baseline and after each cycle of toripalimab treatment. Personalized minimal residual disease (MRD) assays and low-pass whole genome sequencing (LP-WGS) were applied to analyze liquid biopsy samples. **Results:** Eighteen patients (90%) completed all 4 cycles of neoadjuvant treatment. Grade 3-4 immune-related adverse events occurred in two patients (10%). Eight patients (40%) achieved a pathological complete response (pCR). Thirteen patients (65%) had no remaining invasive disease (pCR or pTisN0/pTaN0). Pre-treatment somatic variants and copy number abnormalities were prevalently detected in ucfDNA as compared to bcfDNA. On-treatment urinary tumor DNA (utDNA) clearance was associated with objective responses. Preliminary concordance was observed between molecular and pathological MRD status. **Conclusions:** These findings suggest that neoadjuvant administration of PD-1 blockade followed by surgical resection represents a feasible and efficacious approach to treat MIBC. The exploratory biomarker assessment demonstrates the potential utility of longitudinal personalized utDNA analysis to complement existing trial endpoints. Research Sponsor: National Natural Science Foundation of China (81672514, 81902562, 81922047, 82172596), Shanghai Natural Science Foundation (16ZR1420300, 18410720400, 19431907400), Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20161313).

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Tumor genomic landscape of locally advanced or metastatic urothelial carcinoma with squamous differentiation (UCS) compared to pure urothelial carcinoma (UC).

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Background: UCS is a common entity and usually managed similarly to pure UC but requires focused study. Limited data are available on the genomic profile of UCS. We hypothesized that UCS would have a distinct genomic landscape compared to UC. **Methods:** In this IRB-approved retrospective study, pts) with advanced UCS and UC undergoing tumor based comprehensive genomic profiling from a CLIA-certified laboratory were included. An independent genitourinary pathologist reviewed all cases. Pts were determined to have UCS based on presence of any component of squamous differentiation. Pts with UC having any other secondary histology variant were excluded. Genes with alterations (GA) in less than 5% of pts and variants of unknown significance were excluded from the analysis. test was used to compare gene aberration frequency and the p-values were adjusted for false using Benjamini-Hochberg (BH) correction. **Results:** 87 pts were eligible and included. UCS (n=31) vs UC (n=56): median age, 66 vs 68 years; male vs female: 21/10 vs 48/8Genomic aberrations in both groups are listed in the. GA in *KMT2D* was found to be significantly enriched in UCS vs UC (15/31 vs 0/56, FDR <0.001, p value = <0.001). GA in *CUL4A* was numerically higher in UCS vs UC (4/31 vs 1/56, FDR= 0.444, p-value = 0.03). Tumor mutation burden the frequency of genomic aberrations per pt were not significantly different in the groups. **Conclusions:** While tumor GA in only *KMT2D* was significantly enriched in the UCS cohort, it is interesting to note that both *KMT2D* and *CUL4A* (higher frequency in UCS) are involved in epigenetic regulation. Identification of underlying molecular targets and biomarkers can guide further drug development in this population. Limitations include small sample size, selection and confounding biases. These hypothesis-generating data need external validation. Research Sponsor: None.

Gene	UCS (N = 31)	UC (N = 56)	P-value	BH-Adjusted
TERT	22 (71%)	43 (76.8%)	0.54	0.856
TP53	21 (67.7%)	28 (50%)	0.11	0.572
CDKN2B	14 (45.2%)	19 (33.9%)	0.3	0.629
ARID1A	10 (32.3%)	11 (19.6%)	0.18	0.629
PIK3CA	8 (25.8%)	10 (17.9%)	0.38	0.707
RB1	7 (22.6%)	10 (17.9%)	0.59	0.856
KMT2D	15 (48.4%)	0 (0%)	<0.001	<0.001
FGFR3	3 (9.7%)	11 (19.6%)	0.22	0.629
KDM6A	6 (19.4%)	8 (14.3%)	0.53	0.856

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Tumor genomic landscape in smokers compared to non-smoker patients with locally advanced or metastatic urothelial carcinoma.

Nishita Tripathi, Nicolas Sayegh, Yeonjung Jo, Haoran Li, Roberto Nussenzveig, Benjamin Haaland, Vinay Mathew Thomas, Sumati Gupta, Deepika Sirohi, Umang Swami, Neeraj Agarwal, Benjamin L. Maughan; Huntsman Cancer Institute, Salt Lake City, UT; Huntsman Cancer Institute-University of Utah Health Care, Salt Lake City, UT; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; University of Utah and ARUP Laboratories, Salt Lake City, UT

Background: Cigarette smoking is a known risk factor for bladder cancer. Smokers have been reported to have greater ERCC2-Signature mutations and APOBEC-Signature 13 mutations when compared to non-smokers in a TCGA based study (PMID: 33849962). Our objective was to assess the frequency of targetable genomic alterations in smokers (current or past) vs never smokers patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC). **Methods:** In this IRB approved retrospective study, smokers vs non-smokers pts with mUC undergoing tumor comprehensive genomic profiling (CGP) from CLIA-certified laboratory were included. Genes with alterations (GA) in $<$ 5% pts and variants of unknown significance were excluded from the analysis. A chi square test was used to compare gene frequency aberration and the analysis was adjusted for false discovery using Benjamini-Hochberg (BH) correction. The median number of genomic aberrations per pt was compared using Wilcoxon rank-sum test. **Results:** 137 pts were eligible and included. Smokers (n=70) and non-smokers (n=67): median age, 67 vs 68 years; male vs female: 55/15 vs 42/25. The genomic aberrations enriched in smokers and non-smokers are shown in the table. The most common GA observed in smokers were *TERT, TP53*, *CDKN2B*, *RB1* and *KDM6A;* and non-smokers were *TERT*, *TP53*, *CDKN2B*, *PIK3CA* and *RB1* (Table). Tumor mutation burden and the frequency of genomic aberrations per pt were similar in both groups. **Conclusions:** Herein, we independently validate the findings by Walasek, Almassi et. al. (abstract B20, AACR 2020) of no significant difference in the tumor GA between smokers vs non-smokers pts with advanced urothelial carcinoma, despite high prevalence of targetable genomic aberrations in both cohorts. Future directions should include the investigation of epigenomic changes and transcriptomic profiling to further elucidate the effect of smoking on bladder cancer. Research Sponsor: None.

Gene	Smoker (N = 70)	Non-smoker (N = 672)
TERT	52 (74.3%)	51 (76.1%)
TP53	39 (55.7%)	33 (49.3%)
CDKN2B	21 (30%)	21 (31.3%)
RB1	19 (27.1%)	17 (25.4%)
KDM6A	16 (22.9%)	12 (17.9%)
ARID1A	13 (18.6%)	14 (20.9%)
FGFR3	12 (17.1%)	12 (17.9%)
PIK3CA	7 (10%)	17 (25.4%)
CCND1	10 (14.3%)	9 (13.4%)

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Prognostic impact of serum cytokeratin 19 fragments in patient with metastatic urothelial cancer treated with immune checkpoint inihibitors.

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Background: Recent clinical trials such as Keynote-045, EV-201 and Javelin bladder100 have provided new therapeutic agents for metastatic urothelial carcinoma (mUC). However, the only tool that can evaluate the therapeutic responses is a radiological criteria, Response Evaluation Criteria in Solid Tumors (RECIST) in mUC. In the clinical practice, biomarkers that can predict the efficacy and prognosis of various agents are essential to treat these patients, and the search for such biomarkers is urgently needed. We reported that Performance status ≥ 1, liver metastasis and elevated serum cytokeratin 19 fragments (sCYFRA) are the prognostic factors for first-line cytotoxic cheomotherapy (CTC) for mUC. In this study we evaluated pretreated clinical biomarkers including sCYFRA that can predict overall survival (OS) in patients with mUC treated with immune-checkpoint inhibitors (ICI). **Methods:** Thirty four patients with mUC received pembrolizuab (PB) from February 2018 to July 2020 at our institution. We retrospectively collected performance status, metastasis site, blood neutrophil-lymphocyte ratio (NLR), hemoglobin (Hb), and serum levels of lactose dehydrogenase (LD), alkaline phosphatase (ALP), C-reacted protein (CRP), total protein, albumin, corrected calcium (Ca), carbohydrate antigen19-9, sCYFRA before PB was administered. OS rate were analyzed by Kaplan-Meier curves and log-rank test. Multivariate analysis was carried out using the Cox hazards model. Objective Response rate (ORR) was evaluated based on RECIST (version 1.1). **Results:** Of 34 patients (Pts), with median age of 73(31-86), during the median follow-up period of 25 (7-126) months, 21patients (65%) had died. Median OS was 9.2 months (0.2-33.4), A 1-year OS rate was 33%. ORR was 33% and 9 Pts was SD (27%) and 14 pts (40%) was progressive disease. On univariate analysis, bone metastasis (p=0.028), LD (p=0.003), ALP (p=0.001), Ca (p=0.003) and sCYFRA (p=0.001) were the significant prognostic factor for OS. On multivariate analysis, ALP (HR9.2, 95%CI [2.89-135.9], p=0.002), Ca (HR7.3, (95%CI [2.36-22.49], p=0.001), sCYFRA (HR 5.0, 95%CI [1.63-15.55], p=0.005) were the significant prognostic factor for OS. Based on these 3 factors we divided pts into three groups, good risk (G1,0 factor), intermediate risk (G2, 1 factor) and poor risk (G3, 2-3 factors)3. There was a significant difference between the three groups for OS on K-M curve (G1 vs G2, p=0.001, G2vs G3, p=0.009). **Conclusions:** sCYFRA, ALP and Ca were the independent prognostic factors for OS in patients with mUC treated with ICI. sCYFRA was the independent prognostic factor for OS in the 1st line CTC and 2nd line ICI and it can be a prognostic factor though those therapies. Research Sponsor: None.

Incidence and clinical outcomes of HER2-altered bladder cancer (BC) patients (pts).

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Background: Bladder cancer has one of the highest rates of human epidermal growth factor receptor 2 (HER2) alteration. Novel HER2-directed agents are being investigated in metastatic BC. We sought to define the incidence and clinical characteristics of HER2-altered BC across disease states. **Methods:** We retrospectively analyzed our single-institution, clinically annotated cohort of urothelial BC pts with available genomic profiling data (MSK-IMPACT). We quantified the prevalence of HER2 alterations, defined as driver mutation (based on OncoKB), and/or amplification, across BC disease states. We examined the association between HER2 alteration and disease progression and survival. The Kaplan-Meier method was used for time-to-event analyses. **Results:** A total of 1073 BC pts underwent MSK IMPACT profiling of tumor tissue derived from the following disease states: 36% (n = 380) non-muscle invasive (NMI)BC, 41% (n = 443) muscle invasive (MI)BC, and 23% (n = 250) (met)BC. At initial diagnosis, the median age was 67 years, 77% (n = 822) were male, 86% (n = 928) were white, and 66% (n = 710) were smokers. Overall, 16% (n = 177) of pts had any oncogenic HER2 alteration (Table), including 11% with a HER2 driver mutation and 7% with HER2 amplification The most frequent mutations were S310F (40%, n = 53) and S310Y (14%, n = 19). The rate of HER2 amplification was different among the three groups (p = 0.002), 9% in MIBC and metBC compared to 3% in NMIBC. Among 514 pts with NMIBC, the median time to progression (TTP) to MIBC or metBC was 111.6 months (95% CI: 85.7-NR). Among NMIBC pts, TTP was significantly shorter for HER2-amplified (n = 17) vs. non-amplified (n = 497) (HR = 1.99, 95%CI: 1.05-3.76, p = 0.034, median 26 vs. 114 months). Among pts with metBC receiving frontline platinum-based chemotherapy (n = 143), the median overall survival (OS) was 25.3 months (95%CI: 18.5-33.9). OS was numerically higher in pts with any oncogenic HER2 alteration (n = 26) compared to wild-type (n = 117) (HR = 0.59, 95% CI: 0.33-1.07, p = 0.082), though this difference was not statistically significant. The median OS for platinum-refractory metBC pts receiving 2nd line immunotherapy (n = 63) was 10.3 months (95%CI: 7.2-31.6), and the association between OS and HER2 alteration was not significant (HR = 0.57, 95%CI: 0.24-1.37, p = 0.2). **Conclusions:** HER2 amplification is more frequent in MIBC and metBC than in NMIBC. In NMIBC, HER2 amplification is associated with shorter TTP to MIBC or metBC. HER2 alteration in metBC is associated with a non-significant trend towards improved OS in frontline platinum-treated pts, though this analysis is limited by small sample size. Research Sponsor: None.

Disease State	Overall N = 1,073	metBC N = 250	MIBC N = 443	NMIBC N = 380	p-value
Any HER2 Alteration	177 (16%)	46 (18%)	77 (17%)	54 (14%)	0.3
HER2 Driver Mutation	115 (11%)	26 (10%)	45 (10%)	44 (12%)	0.8
HER2 Amplification	76 (7.1%)	22 (8.8%)	41 (9.3%)	13 (3.4%)	**0.002**

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Prognostic value of HER2 expression levels for upper tract urothelial carcinoma.

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Background: HER2 expression is an adverse prognostic factor of bladder urothelial carcinoma (UBC) while the prognostic value of HER2 expression in upper tract urothelial carcinoma (UTUC) remains to be explored. This study aims to investigate the prognostic value of different HER2 expression and gene amplification levels in UTUC. **Methods:** The baseline clinicopathological data of 130 patients with UTUC were reviewed. The expression level of HER2 was detected by immunohistochemistry (IHC) staining (Anti-Her2/neu, Cat.4B5, Ventana) from formalin-fixed paraffin-embedded (FFPE) tumor tissue of patients. The HER2 gene amplification level was detected by second-generation sequencing (NGS) (HER2 gene copy number [CN]) or Fluorescence in situ hybridization (FISH) from FFPE tumor tissue of patients. HER2 negative was defined as IHC 0. HER2 low expression was defined as IHC 2+ but CN- or FISH-, while HER2 overexpression included IHC 3+, and IHC 2+ but CN+ or FISH+. The correlation between HER2 expression levels or other clinicopathological characteristics and overall survival (OS) were analyzed. The Cox proportional-hazards model was used to analyze the independent prognostic factors of UTUC. **Results:** All the 130 patients provided FFPE tumor slides for the IHC detection of the HER2 expression levels including: IHC 0 (n = 47), IHC 1+ (n = 28), IHC 2+ (n = 41) and IHC 3+ (n = 14), the median OS were 27.5 months, 48.7 months, 67.3 months, and not reached, respectively, with significantly difference ($P = 0.014$). Among the 41 patients with HER2 IHC 2+, 15 patients received the detection of the HER2 gene amplification level by NGS or FISH while the other 26 patients whose HER2 gene amplification levels were unknown were excluded from the analysis. The patients of HER2 negative, low expression, and overexpression had a median OS of 27.5 months, 58.0 months, and 60.0 months, respectively, but the difference was not significant ($P = 0.184$). Cox proportional-hazards model also verified that the HER2 IHC expression is an independent prognostic factor on the survival, while the prognostic value of the HER2 gene amplification levels was not found. **Conclusions:** HER2 IHC expression is an independent factor for the prognosis of patients with UTUC. However, HER2 gene amplification levels have no impact on the prognosis of UTUC patients. HER2 expression especially the HER2 gene amplification level in UTUC needs to be explored further. Research Sponsor: National Natural Science Foundation of China (NO.82172604).

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Multiplexed autoantibody (AA) profiling of patients (pts) with metastatic urothelial carcinoma (mUC) receiving immune checkpoint inhibitors or platinum-based chemotherapy.

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Background: The AA profile may be altered in malignancies and provide insights into tumor biology and the immune state. We hypothesized that the longitudinal AA profiling of mUC pts receiving an immune checkpoint inhibitor (ICI) may provide insights into the immune response, which may be associated with immune events and help discover new therapeutic targets. **Methods:** We utilized serum from mUC pts receiving an ICI or platinum-based chemotherapy (PBC) at the Dana-Farber Cancer Institute. Age and sex matched healthy controls were also studied. The SeroTag immuno-oncology discovery array (Oncimmune) was utilized, with quantification of the AA reactivity towards 1150 antigens. Bound autoantibodies were detected using an anti-IgG-specific detection antibody conjugated to the fluorescent reporter dye phycoerythrin. The AA reactivity was reported as the median fluorescence intensity (MFI) for each color and sample using a Luminex FlexMAP3D analyzer. A significance analysis of microarrays was performed to identify AAs with elevated levels in bladder cancer compared to matched healthy controls (HCs). AAs with > 1.5 increase between pre- and post-treatment were reported. Scatter and box-whisker plots were reported for all pts and antigens, respectively. **Results:** Pre- (n = 66) and post treatment (n = 65) serum samples were available from mUC pts receiving pembrolizumab (n = 25), atezolizumab (n = 21), nivolumab (n = 5), avelumab (n = 1), durvalumab + tremelimumab (n = 1), nivolumab plus vaccine (n = 1), and 12 pts who received PBC (cisplatin n = 8, carboplatin n = 4). The median duration between the pre- and post-therapy samples was 6 months, median age was 67.7 years (range 40-91) with 51 men (77.3%). Overall, significant heterogeneity of AAs between pts was observed with 37 AAs showing higher reactivity in pre-treatment mUC pts vs. 47 HCs, notably anti-CTAG1 (NY-ESO-1), CTAG2 (NY-ESO-2), MAGE B-18, KRAS, GRB2, RARRES2, HSP72 and FGFR3 (all $p < 0.05$). Pre- and post-therapy AA profiles were similar with unique changes seen in each patient. Notably, 3 pts receiving an ICI developed AAs to NY-ESO-1. Pts receiving PBC less frequently developed new AAs, although pts treated with cisplatin appeared to develop AAs more frequently compared to carboplatin-treated pts. **Conclusions:** This is the first report of a comprehensive AA profile using a novel platform in mUC pts. The study identified multiple elevated AAs in mUC pts vs. HCs, most notably NY-ESO-1, which also developed in some pts following ICIs. Pts treated with PBC did not develop new AAs frequently, although there appeared to be a difference between cisplatin and carboplatin-based chemotherapy. Further development of this platform is warranted to provide data that is orthogonal to genomic/transcriptomic profiling and shed insights on potential therapeutically actionable antigens. Research Sponsor: Oncimmune.

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Integrative analysis of urine cell-free DNA for the detection of residual disease in localized bladder cancer patients.

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Background: We previously developed a liquid biopsy assay to measure urine tumor DNA (utDNA) levels based on detection of single nucleotide variants (SNVs) in urine cell-free DNA (cfDNA). Nonsilent SNV detection in urine from muscle-invasive bladder cancer (MIBC) patients prior to radical cystectomy (RC) was associated with pathologic residual disease and worse progression-free survival (Chauhan et al., *PLOS Medicine*, 2021). Given the multiple types of genomic alterations present in bladder cancer (BC), here we developed a multi-omics approach for estimating utDNA levels without restricting our approach to SNVs. We performed ultra-low pass whole genome sequencing (ULP-WGS) based copy number analysis and urine Cancer Personalized Profiling by deep Sequencing (uCAPP-Seq) of urine cell-free DNA to predict pathologic complete response (pCR) in localized BC patients. **Methods:** We acquired urine preoperatively from 65 BC patients (69% muscle-invasive) on the day of standard-of-care RC, and after neoadjuvant chemotherapy in 48% of patients. We performed ULP-WGS of urine cfDNA from all 65 BC patients and 11 healthy adults. utDNA levels based on genome-wide copy number alterations (CNAs) in urine cfDNA was estimated using ichorCNA. In order to derive a SNV-based utDNA level as well, uCAPP-Seq was applied to urine cfDNA samples derived from 42 patients using a 145 kb panel of 49 consensus driver genes commonly mutated in MIBC. **Results:** In our cohort of 65 BC patients, 55% of patients achieved pCR ($n = 36$) while 45% had residual disease detected in their surgical sample (no pCR; $n = 29$). Comparing ULP-WGS-derived utDNA levels between the groups, patients with no pCR had significantly higher CNA-derived tumor fractions in urine compared to patients with pCR (median 8.9% vs 1.8%, $p = 0.01$) and healthy adults ($n = 11$) (median 8.9% vs 0%, $p = 0.006$). Further analysis with uCAPP-Seq in 42 patients revealed that nonsilent SNV-based utDNA detection correlated significantly with the absence of pCR ($p < 0.001$) with a sensitivity of 81% and specificity of 81%. Moreover, utDNA-positive patients exhibited significantly worse progression-free survival compared to utDNA-negative patients (HR = 7.4; 95% CI: 1.4–38.9; $p = 0.02$). **Conclusions:** Bladder cancer patients who did not attain a pCR at the time of RC had greater genome-wide copy number alterations and nonsilent single nucleotide variants in their urine cfDNA compared to patients with pCR. These results suggest that integrative multi-omics of urine derived from MIBC patients has potential real-world clinical impact for bladder-sparing approaches in select patients. Research Sponsor: U.S. National Institutes of Health, Other Foundation, U.S. National Institutes of Health, V Foundation.

Association of leucocyte levels in urine with tissue PD-L1 status and immune infiltration into basal bladder cancer subtype in the prospective real-world clinicopathological register trial Bladder BRIDGister.

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Background: The objective of the present study was to evaluate whether preoperative standard urine parameters such as leucocyte count in urine samples dominate in particular molecular subtypes of bladder cancer and reflect the immune infiltration status in the tissue in matched urine and TUR biopsy samples from patients being suspicious of bladder cancer and undergoing first TURB within the prospective Real World Experience registry trial "BRIDGister". **Methods:** For this pilot study paraffin fixed pretreatment tissue samples from the first TURB of 48 pts participating in the BRIDGister trial and matched urine samples were prospectively collected and analyzed. RNA from FFPE tissues were extracted by commercial kits- Relative gene expression of subtyping markers (KRT5, KRT20) by standardized RT-qPCR systems for PD-1, PD-L1, CTLA4 (STRATIFYER Molecular Pathology GmbH, Cologne). In addition urine samples were analyzed for leucocyte and erythrocyte count. Spearman correlation, Kruskal-Wallis, MannWhitney and Sensitivity/Specificity tests were done by JMP 9.0.0 (SAS software). **Results:** The pilot cohort of the BRIDGister trial consisted of 48 patients (median age: 77, male 65% vs. female 35%) of diverse clinical stages (Benign lesions/no tumor 38%, pTa 23%, pT1 20%, pT2 19%) and WHO 1973 grade (G1 11%, G2 43%, G3 23%). Presence of leucocytes but not erythrocytes was negatively associated with KRT20 (r=-0.4249, p=0.0216) but positive with KRT5 (r=0.3704, p=0.0479). Moreover high levels of leucocytes in urine were positively associated with tumor expression of PD-L1 (r=0.5081, p=0.0041), PD-1 (r=0.5342, p=0.00024) and CTLA4 (r=0.4244, p=0.0194). In contrast there was no significant association of tumor PDL-1, PD-1 and CTLA4 expression with erythrocyte count in urine. **Conclusions:** Presence of leucotytes in urine is strongly associated with basal subtype and immune cell infiltration into early bladder cancer. As the presence of erythrcytes did not reveal these significant associations, the presence of leucocytes is not due to simple bleeding or tissue vulnerability. Moreover, the strong tumor subtype specificity further demonstrate the basal tumor specificity of urine leucocytes and therefore may be helpful for detecting and monitoring basal bladder cancer in a non invasive fashion. Given the prognostic value of tissue determination of PD-L1, PD-1 and CTLA4 quantitation on mRNA level, these results warrant further investigation to conclude on its impact on outcome prediction (BCG responsiveness, recurrence, progression, etc.), which will be prospectively analyzed in the framework of the ongoing multicenter BRIDGister Real World Experience trial. Research Sponsor: None.

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Association between *TERT* promoter mutations and clinical outcome with immune checkpoint inhibitor therapy for advanced urothelial cancer.

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Background: Recently published data suggests that the presence of a *TERT* promoter mutation is predictive of superior overall survival (OS) in patients (pts) with advanced/metastatic bladder cancer (mUC) treated with an immune checkpoint inhibitor (ICI) (Kouchkovsky *et al*, JITC 2021). We aim to validate the results of this study in a large independent cohort. **Methods:** Pts with mUC treated at two tertiary cancer centers with available genomic data collected in the course of routine clinical care were identified retrospectively. Pts that had received at least one line of ICI therapy in the metastatic setting were selected. Demographic and treatment data were collected, with pts divided into two groups based on the presence or absence of *TERT* mutation status (*TERT*m or *TERT*wt, respectively). We evaluated OS from diagnosis of at least muscle invasive disease, progression free survival (PFS), and objective response rate (ORR) with ICI therapy across the two groups. OS in our cohort was compared with findings from pts with bladder cancer in The Cancer Genome Atlas (TCGA) database. **Results:** From our combined data sets, a total of 166 pts had available genomic data, with 64 *TERT*m pts (52:12 M:F) and 58 *TERT*wt pts (32:26 M:F) meeting criteria for inclusion. Median age at diagnosis was 67 in both groups. The site of primary disease was bladder in 54 (84%) *TERT*m vs. 41 (71%) in *TERT*wt; 10 (16%) and 17 (29%) had upper tract disease, respectively. 47 (73%) *TERTm* pts and 40 (69%) *TERT*wt pts had pure urothelial disease; 17 (27%) and 18 (31%) pts had mixed/pure variant histology, respectively. 37 (58%) and 42 (72%) pts received first-line ICI therapy whereas 27 (42%) and 16 (28%) received subsequent-line therapy in *TERT*m and *TERT*wt, respectively. At the time of analysis, there were 24 (38%) patients alive in *TERT*m, and 23 (40%) patients alive in *TERT*wt. OS was 35 vs. 36 mos (95% CI 0.62-1.51, P=0.66) in *TERT*m and *TERT*wt, respectively. PFS on ICI therapy was 4.6 vs. 5.3 mos (95% CI 0.58-1.34, P≥0.99) in *TERT*m and *TERT*wt, respectively. ORR was 75% in *TERT*m and 50% in *TERT*wt (P=.004). OS in the TCGA database was 35 mos in *TERT*m and 47 in *TERT*wt (P=0.19) from a total of 311 and 127 pts, respectively. **Conclusions:** In contrast to previously published data, our data show no difference in OS and PFS on the basis of *TERT* mutational status in pts with mUC treated with ICI therapy. Further analysis from larger datasets is needed to reconcile the role of *TERT* mutations within this patient population. Research Sponsor: None.

Genomic characterization and identification of actionable variants in patients with locally advanced or metastatic urothelial carcinoma (mUC).

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Background: Next generation sequencing (NGS)-based molecular profiling has been widely used across various tumor types including genitourinary malignancies to better understand and potentially predict tumor behavior. The goal of this study was to determine the feasibility of using NGS to characterize mUC and to identify potentially actionable variants. **Methods:** Patients with locally advanced or metastatic urothelial carcinoma (mUC) treated at the Princess Margaret Cancer Center were prospectively recruited for the OCTANE study, which collects archival tumor samples to provide genomic characterization through NGS with a custom hybridization capture DNA-based panel (555 genes) or a targeted DNA/RNA amplicon panel (Oncomine Comprehensive Assay v3, 161 driver gene panel). Variants were annotated using a somatic variant scheme [PMID: 25880439] or the oncoKB database. Comprehensive clinical information including patient, disease and treatment characteristics was collected using electronic patient records. Kaplan-Meier and cox regression were used for survival analysis. **Results:** Of the 73 patients, median age was 65 (23-83), majority were men (69%), most had lower tract disease (80%) and 41% had de novo metastatic disease. NGS was deemed feasible, based on availability of tumor samples, and performed in 67 (92%) patients. Overall, 61 (91%) had at least one oncogenic variant, including 34 (56%) with a potentially "druggable" target. The most frequent genomic alterations found were TP53 (44%), FGFR (18%), TERT (18%), ARID1A (18%) and PIK3CA (16%), all classified as "pathogenic/likely pathogenic". Only 2 patients received targeted treatment, one as part of clinical trial and one as standard of care. mOS was numerically longer among patients with genomic mutations compared to the ones without: 55 vs 31 months (HR: 0.87, CI 95% 0.3-2.4; p:0.7). No specific mutation was shown to significantly impact survival (table). **Conclusions:** Use of NGS technology in characterizing the genomic profile of patients with locally advanced or metastatic UC was feasible in most cases. Oncogenic variants were detected in the majority of patients, and more than half of them harbored a potentially "druggable" target, which may lead to future therapeutic advances. Research Sponsor: Government of Ontario, the Princess Margaret Cancer Foundation.

Mutation	mOS in mutation positive versus negative	HR (95% CI)	P value
TP53	72 mos vs. 36 mos	0.56 (0.2-1.1)	0.09
FGFR	55 mos vs 48 mos	0.6 (0.2-1.2)	0.19
TERT	43 mos vs. 48 mos	0.7 (0.2-1.9)	0.54
ARID-1	55 mos vs 48 mos	0.6 (0.2-1.5)	0.32
PIK3CA	38 mos x 55 mos	1.8 (0.7-4.5)	0.16

mOS: median overall survival; HR: hazard ratio.

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Impact of PD-L1 expression on conventional urothelial bladder carcinoma (UBC) genomic alteration (GA) profile.

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Background: Immunohistochemistry (IHC) to determine PD-L1 expression level has been proposed a companion assay related to the approval of immune checkpoint inhibitors in UBC. We hypothesized that the GA profiles would differ between UBC featuring high vs negative PD-L1 expression. **Methods:** 102 cases of advanced UBC with known PD-L1 expression underwent hybrid-capture based comprehensive genomic profiling to evaluate all classes of GA. Tumor mutational burden (TMB) was determined on up to 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 114 loci. Tumor cell (TC) PD-L1 expression was determined by IHC (Dako 22C3). Only PD-L1 high (H) (≥50% TC expression) and negative (N) (0% TC expression) cases were included with PD-L1 Low (1-49% TC expression) cases excluded from this study. **Results:** Overall, only 2 (8.3%) of the 24 PD-L1H UBC featured *CD274* (*PD-L1*) amplification (mean 19 copies) and none of 78 PD-L1N had CD274 amp (P =.05). The gender, age was similar in the groups. When compared with the PD-L1H UBC cases, FGFR3 GA were significantly more frequent in the UBC PD-L1N cases (p =.02). Currently "untargetable" GA that were more frequent in the PD-L1H UBC, but did not reach statistical significance, included *TP53*, *TERT* and *RB1*. *MTAP* loss, a potential target for PRMT5 and MTA2 inhibitors, were 3X more frequent in the PD-L1N UBC. *ERBB2* amplification and *ERBB3* and *PIK3CA* short variant (SV) GA were more frequent in the PD-L1N UBC with differences not reaching significance. Other ICPI-associated potential biomarkers, including MSI status, TMB level and GA in *PBRM1*, *STK11* and *MDM2* were not significantly different in the groups. For UBC cases where a mutational signature could be determined, 10/12 (83%) of PD-L1H and 21/29 (72%) of PD-L1N UBC featured APOBEC signature; 2 PD-L1N featured MMR signature and 6 PD-L1N UBC featured no dominant signature. **Conclusions:** PD-L1H and PD-L1N subtypes of UBC differ in their genomic profiles:PD-L1N UBC features greater frequencies of potentially "targetable" GA, including *FGFR3*, *ERBB2*, *ERBB3* and *PIK3CA*. PD-L1 IHC may thus not only play a role in the selection of ICPI for advanced UBC but also in designing trials that may combine ICPI with targeted therapies. Limitations include small sample size, possible selection bias and lack of clinical annotation. Research Sponsor: Foundation Medicine Inc.

	UBC High PD-L1 Expression (24 cases)	UBC Negative PD-L1 Expression (78 cases)	P Value
TP53	75.0%	50.6%	NS
TERT	91.7%	77.2%	NS
MTAP Loss	8.3%	25.3%	NS
ERBB2 amplification	4.2%	15.2%	NS
ERBB3	4.2%	10.1%	NS
FGFR3	4.2%	26.6%	=.02
CD274 amplification	8.3%	0%	=.05
MSI High Status	0%	1.3%	NS
TMB≥10 mut/Mb	50%	34.6%	NS

Upper tract urothelial carcinoma transcriptome profiling and immune microenvironment characterization.

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Background: Upper tract urothelial carcinoma (UTUC) is an aggressive disease that is risk-stratified by clinicopathological factors due to an incomplete understanding of its molecular features. Thus, we performed transcriptomic profiling of UTUC tumors from radical nephroureterectomy specimens and compared their molecular characterization to survival outcomes. **Methods:** 100 UTUC tumors from 100 patients were subject to RNA sequencing and a hybridization capture-based assay for deep sequencing of cancer-associated genes, followed by unsupervised nonnegative matrix factorization clustering based on the top 10% of variant genes. Gene Set Enrichment and immune deconvolution analyses assessed for differences in the tumor microenvironments (TME) between clusters. **Results:** Consensus clustering analysis identified 5 biologically distinct clusters (Cluster 1 (C1) = 17, C2 = 18, C3 = 30, C4 = 11, and C5 = 24 patients), which were associated with significant differences in disease-free (DFS) ($p < 0.01$) and overall survival (OS) ($p = 0.03$). C1 and C2 were associated with pT3/4 stages and worse DFS and OS, while C5 was associated with pTa/1 stages and better DFS and OS. In terms of somatic mutation frequency differences, C3 and C4 had overall higher tumor mutation burden and mutations in epigenetic modulators, which corresponds with the transcriptomic finding of higher microsatellite instability expression signatures in these two clusters as well. Of note, all Lynch patients (N = 4) were in C3. C3 was enriched for the presence of FGFR3 driver mutations in 93% of tumors, and TP53 mutations were frequent in C2 and C4 in 47 and 55% of tumors, respectively. Differentially expressed genes and Gene Set Enrichment analyses revealed that C1 and C2 were enriched with several Hallmark inflammation signatures, such as TNF-α signaling via NF-kB, allograft rejection, inflammatory response, IL6 JAK/STAT3 signaling, and IL2 STAT5 signaling. C1 demonstrated a particularly inflammatory phenotype enriched with INF-γ and INF-α response gene sets. Lastly, in the TME deconvolution analysis, C1 and C2 had higher expression of PDL-1, immune checkpoint, immune suppression, cancer-associated fibroblasts, and myeloid inflammation surrogate signatures. C2 and C3 were enriched with CD8 T-cells, while C1 was enriched for INF-γ and hypoxia signatures. C2 had the least hypoxic TME, which may be related to stronger stromal, EMT, and angiogenesis signature signals seen. These results were then validated using an outside institution's published cohort. **Conclusions:** Several differences in transcriptomic features indicate heterogeneity among UTUC tumors. Two clusters with high rates of recurrence and worse prognosis are associated with higher immune and myeloid cell infiltration. In addition to clinicopathologic factors, tumor microenvironment immune features may have potential use for disease prognostication. Research Sponsor: Thompson Family Foundation, Other Government Agency, U.S. National Institutes of Health.

Comprehensive metabolomic profiling of plasma from patients (pts) with metastatic urothelial carcinoma (mUC) receiving immune checkpoint inhibitors (ICI) or platinum-based chemotherapy (PBC).

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Background: Metabolomic profiling of plasma from mUC pts has not been comprehensively examined. Plasma metabolomics may capture the effects of interactions between the malignancy, host and therapy. We hypothesized that Identifying metabolites in plasma from patients with mUC receiving an ICI or PBC may shed valuable insights regarding tumor biology and mechanisms of resistance. **Methods:** We obtained 0.2 ml plasma before and after starting therapy from pts with mUC receiving an ICI or PBC at the Dana-Farber Cancer Institute. Plasma metabolomic profiling was conducted at the Broad Institute using 3 complementary liquid chromatography tandem mass spectrometry (LC-MS)-based metabolomics platforms. We measured 648 metabolites at baseline prior to starting ICI/PBC and at a second time point in each subject following initiation of ICI/PBC. Metabolite levels were assumed to be normally distributed with log transformation to transform distributions to be approximately symmetric. We performed Wilcoxon-rank sum test to compare the levels of metabolites before and after initiation of the ICI or PBC (significance at $p < 0.05$). **Results:** Plasma was available at baseline and during therapy in 53 mUC pts (ICI: n = 43; PBC: n = 10). The median age was 68 (range: 39-86) years and 42 (82.3%) were male. The median time from baseline to the second time point was 4.7 months (range: 0.7-90.2). The ICIs administered were atezolizumab (n = 20), pembrolizumab (n = 16), nivolumab (n = 5), and durvalumab + tremelimumab (n = 1). We identified 20 metabolites that were significantly increased in post-PBC plasma samples (vs. pre-PBC) and 19 metabolites increased in post-ICI (vs. pre-ICI) samples ($p < 0.05$). All altered metabolites except one (Uracil) were exclusive for each treatment group. The most significant metabolites that increased following initiation of the ICI and PBC are shown in the Table. Evaluation of the association of plasma metabolomics with clinical outcomes and toxicities is ongoing. **Conclusions:** This is the first report, to our knowledge, of comprehensive metabolomic plasma profiling of pre- and post-ICI and PBC pts with mUC. The metabolomic changes after ICI appear distinct from those seen after PBC. Furthermore, our study sheds insights on potential mechanisms of resistance and new therapeutic targets in pts with mUC. Research Sponsor: None.

	ICI		PBC	
Metabolite	**Fold Change**	**p-value**	**Fold Change**	**p-value**
Sorbitol	1.6	0.03	1.2	0.7
Hydroxy-dehydro-nifedipine	1.6	0.01	1.4	0.7
2-Methylbutyroylcarnitine	1.6	0.002	1.0	1.0
5-Hydroxy-tryptophan	1.6	0.01	0.9	0.8
Ceramide 18:1;O2/15:0	1.1	0.78	2.1	0.01
Phosphatidylserine 34:0	0.9	0.27	2.0	0.01
Ceramide 18:1;O2/20:1	1	0.46	1.9	0.02
Phosphatidylethanolamine 38:6	0.9	0.96	1.9	0.02

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A murine MODEL of e-cigarettes exposure to evaluate the carcinogenic effects of vaping on the bladder urothelium.

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Background: Data evaluating the carcinogenic potential of e-cigarette (ECS) by-products on the bladder urothelium is scarce, and to date, no group has studied the direct impact of ECS on the urothelium at the genomic and epigenetic level. While it has been published that ECS exposure causes bladder hyperplasia in mice, no bladder tumors formed and the field is therefore lacking appropriate preclinical models to be able to study ECS related bladder cancer. Importantly, whole organ mapping studies of tumor bearing human bladders have identified DNA methylation field changes in "adjacent normal" urothelium as early events in bladder carcinogenesis. Whether ECS exposure results in early field alterations of DNA methylation in the urothelium is unknown. **Methods:** Mice (4 females, 4 males; 35 weeks old) were exposed to 12% nicotine (120mg/ml) in 1:1 polyethylene glycol: vegetable glycerol (PG/VG) or vehicle (PG/VG) daily: 3 hr sessions, 3 sec vape duration, 10 min interval between vapes. Nicotine and cotinine serum concentrations were measured at 3 hrs, and then at 5 days using LC-MS. Bladders were harvested after 4 weeks. DNA was extracted from microdissected urothelial layer. Reduced representation bisulfite sequencing (RRBS) was performed (Zymo Research) using 100ng of DNA input and paired-end chemistry. Alignment was performed using Bismark. Number of loci covered by each sample was determined and data was filtered to only include loci with $>$ 10 reads. Differentially methylated loci were determined. Adjusted p-value $<$ 0.01 was used as threshold to generate heatmaps. Gene Set Enrichment Analysis was performed to contextualize the DNA methylation changes. **Results:** Acute and repeated exposure resulted in significantly higher levels of nicotine and cotinine serum concentration in the nicotine group vs. the vehicle group without significant adverse events. No tumors were observed on gross visualization at the time of urothelium harvest. The number of loci in the RRBS libraries with $>$ 10 reads ranged from 130,000 to 250,000. 53 loci were differentially methylated between nicotine and vehicle. These loci did not correspond to the top hyper/hypo methylated genes in premalignant bladder tissue from recently reported whole-cystectomy mapping. **Conclusions:** We established an effective and safe murine model of ECS exposure closely resembling the human experience of vaping. Significant changes of DNA methylation were observed in mice exposed to ECS vapor vs. a vehicle control after four weeks of daily exposure. Ongoing experiments include longer vaping exposures as well as comparison of RRBS to a recently developed commercial mouse methylarray. Understanding epigenetic and genomic changes as a result of ECS exposure in preclinical models can serve as a foundation for studies developing assays to identify ECS users whose bladders contain early field defects that may place them at higher risk for bladder cancer. Research Sponsor: U.S. National Institutes of Health, University of North Carolina Lineberger Innovation Award 2020.

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Human epidermal growth factor receptor 2 (HER2) and fibroblast growth factor receptor 3 (FGFR3) mutations to reveal biological pathways in urothelial carcinoma.

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Background: Human epidermal growth factor receptor 2 (HER2) (gene name: *ERBB2*) is a member of the epidermal growth factor receptor (EGFR) family and when mutated, associated with higher grade and stage of localized bladder cancer. Two HER2-targeted antibody-drug conjugates (ADC), trastuzumab emtansine and trastuzumab deruxtecan, are currently approved by the Food and Drug Administration (FDA) for use in gastric/breast cancers with promising application in urothelial carcinoma. Fibroblast growth factor receptor 3 (*FGFR3)* is the target of another FDA-approved tyrosine kinase inhibitor erdafitinib and generally associated with more favorable prognosis as well as upper tract carcinoma. The purpose of this study is to characterize *ERBB2* and *FGFR3* mutations in a prospectively collected cohort of urothelial cancers. **Methods:** Patients with localized upper or lower tract urothelial carcinoma diagnosed between 2014 and 2020 who underwent a targeted exome sequencing panel of up to 468 cancer genes were identified. If multiple tumors were sequenced, only the diagnostic specimen was included. Analysis of gene alterations, frequency, and associated co-mutations was performed. Descriptive statistics were used to compare baseline patient characteristics. **Results:** 381 unique *ERBB2* or *FGFR3* mutated urothelial carcinoma specimens were included in this study. Of note, *ERBB2* and *FGFR3* mutations were essentially mutually exclusive and included 122 (66%) *ERBB2* mutated tumors and 259 (34%) *FGFR3* mutated tumors. Patients with tumors harboring *FGFR3* mutations were younger (median 70 years IQR 60-76 vs. 74 years IQR 66-78, $p<0.05$), while patients with *ERBB2* mutated tumors were more likely to be male (85% vs 73%, $p<0.05$). At the time of diagnosis, *ERBB2* tumors were more likely to present with advanced (pT2 or higher) disease compared to *FGFR3* mutated tumors (48% vs 24%). *ERBB2* mutated tumors were more likely associated with *RB1*, *P53*, and *ARID1A* mutations, while *FGFR3* mutated tumors were more likely associated with *CDKN2A/B* and *STAG2* mutations (Table). **Conclusions:** These data highlight divergent biological pathways for patients with targetable mutations in *ERBB2* and *FGFR3* and are consistent with prior findings in non-muscle invasive bladder cancer. *ERBB2* mutated tumors are associated with male gender, more aggressive pathological features and co-mutations with *RB1*, *P53*, and *ARID1A.* Research Sponsor: U.S. National Institutes of Health.

Gene	ERBB2	FGFR3	Log Ratio	p-Value	Enriched in
RB1	38 (31.40%)	5 (1.93%)	4.02	3.20E-16	ERBB2
TP53	63 (52.07%)	54 (20.85%)	1.32	1.54E-09	ERBB2
MCL1	16 (13.22%)	4 (1.54%)	3.1	7.42E-06	ERBB2
CDK12	24 (19.83%)	14 (5.41%)	1.88	2.79E-05	ERBB2
ARID1A	53 (43.80%)	60 (23.17%)	0.92	4.38E-05	ERBB2
CDKN2A	20 (16.53%)	100 (38.61%)	-1.22	7.33E-06	FGFR3
CDKN2B	15 (12.40%)	84 (32.43%)	-1.39	1.38E-05	FGFR3
STAG2	12 (9.92%)	65 (25.10%)	-1.34	2.939E-04	FGFR3

Clinical pharmacology of the antibody-drug conjugate enfortumab vedotin in advanced urothelial carcinoma and other malignant solid tumors.

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Background: Enfortumab vedotin (EV) is an antibody-drug conjugate comprised of a fully human monoclonal antibody directed against Nectin-4 and monomethyl auristatin E (MMAE), a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. EV is approved in the US for treatment of adult patients (pts) with locally advanced/metastatic urothelial carcinoma (la/mUC) who previously received a PD-1/L1 inhibitor and platinum-based chemotherapy, and who are ineligible for cisplatin-based chemotherapy and previously received 1+ lines of therapy. In EV-301, EV significantly reduced risk of death by 30% vs chemotherapy in pts with treated la/mUC. Data from five clinical studies (N = 748) were used to describe the clinical pharmacology of EV. **Methods:** Pharmacokinetics (PK) of EV and free MMAE were studied in pts with la/mUC (n = 699) and malignant solid tumors receiving EV in phase 1, 2, and 3 studies. EV and MMAE PK parameters were calculated with non-compartmental analysis. Population PK analysis was used to characterize/assess impact of covariates on EV and MMAE PK. Antitherapeutic antibodies (ATA) were assessed in all studies. **Results:** EV 0.5 to 1.25 mg/kg IV on Days 1, 8, and 15 of a 28-day cycle showed linear, dose-proportional PK. Mean EV and MMAE clearance was 0.110 and 2.11 L/h, respectively; elimination $t_{1/2}$ was 3.6 and 2.6 days. Steady state was reached by Cycle 1; accumulation was limited for EV and MMAE between cycles. EV PK differences in special populations were not considered clinically meaningful. For renal impairment, no significant differences in exposure of EV and MMAE were observed in mild (n = 272), moderate (n = 315), or severe (n = 25) impairment vs normal renal function. For hepatic impairment, bilirubin was a significant covariate for MMAE only; pts with mild impairment (n = 65) had a 37% increase in $AUC_{0\text{-}28d}$ and 31% increase in C_{max} of MMAE vs pts with normal hepatic function. No clinically significant differences in EV and MMAE PK were observed based on age (range, 24-90 yrs; $>$ 65 yrs, 60%), sex (male, 73%), or race/ethnicity (White, 69%; Asian, 21%; Black, 1%; others/unknown, 8%). Weight-based dosing showed similar exposure for all pts. EV did not prolong mean QTc interval to a clinically relevant extent per ECG/PK data from the EV-102 study (n = 17; advanced UC). Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase MMAE exposure and may increase the risk of adverse events. Following EV 1.25 mg/kg, 16/590 (2.7%) pts tested positive for ATA against EV at $\geq$1 postbaseline time point. **Conclusions:** Integration of EV and free MMAE PK findings support the EV dose of 1.25 mg/kg on Days 1, 8, and 15 of a 28-day cycle. No dose adjustments were required for special populations or by age, sex, or race. Caution is advised during concomitant treatment with strong CYP3A4 inhibitors, and a low rate of immunogenicity was observed. Research Sponsor: Astellas Pharma, Inc.

Initial results of a phase II study of nivolumab(N) and ipilimumab(I) in genitourinary malignancies with neuroendocrine differentiation.

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Background: Patients with metastatic genitourinary malignancies with neuroendocrine have limited therapeutic options following platinum therapy. Given encouraging results in initial cohort analysis for small cell urinary tract carcinoma, a cohort of any genitourinary malignancy with neuroendocrine differentiation was added to a multicenter, single arm, multi-cohort phase II trial to evaluate the efficacy of N and I in this setting. (NCT 03333616) **Methods:** Eligible patients had metastatic or locally advanced genitourinary malignancy with neuroendocrine differentiation with an ECOG performance status of 0-2; they may have received any line of prior therapy excluding prior immunotherapy. Patients underwent baseline biopsy and received treatment with N 3 mg/kg and I 1 mg/kg intravenously every 3 weeks for 4 cycles with continued maintenance of N 480 mg IV every 4 weeks. Imaging was performed at 12 weeks and then every 8 weeks through month 6 and then every 12 weeks thereafter. The primary endpoint was investigator assessed objective response rate (ORR) by RECIST 1.1. **Results:** A total of 27 patients were enrolled between 06/27/2018 and 06/21/2021, 10 (37%) had urinary tract cancer and 17 (63%) had prostate cancer (19 in expansion cohort, 3 urinary tract and 5 prostate cancer from earlier cohorts). The majority (n=25, 93%) patients received prior systemic therapy. Nine (33%) patients received all 4 doses of N and I during the induction period. Nine (33%) patients (7 of whom received 4 cycles N+I) received N maintenance (median number of cycles 9 (range, 2-37)). Median follow-up was 6.8 (range, 0.9-37.3) months. Objective response was achieved in 8 (30%, 80% CI 18%-44%) patients (Table). Median duration of response was not reached with 4 patients maintaining response $>$9 months. Median progression-free survival time was 2.6 (95% CI 1.8-6.5) months At time of analysis, 13 (48%) death events were reported due to progressive disease, in which 3 were bladder and 10 were prostate cancer. 8 (30%) patients developed treatment-related grade 3 or higher toxicities; one grade 5 toxicity was deemed treatment-unrelated. **Conclusions:** In this study we demonstrate N+I resulted in objective responses in patients with genitourinary malignancy with neuroendocrine differentiation. ORR of 50% in small cell carcinoma is bladder cancer is noteworthy and will be evaluated further in ongoing expansion cohort of bladder or upper tract carcinoma with variant histology. Clinical trial information: NCT03333616. Research Sponsor: BMS.

Response summary.

	Overall (N=27, %)	Urinary Tract (N=10, %)	Prostate (N=17, %)
CR	2 (7)	2 (20)	0 (0)
PR	6 (22)	3 (30)	3 (18)
SD	1 (4)	0 (0)	1 (6)
PD	17 (63)	5 (50)	12 (70)
NE	1 (4)	0 (0)	1 (6)
ORR (CR+PR)	8 (30, 80% CI: 18-44)	5 (50, 80% CI: 27-73)	3 (18, 80% CI: 7-35)

CR – Complete response, PR – Partial Response, SD – Stable disease, PD – Progressive PD, NE – Not evaluable.

Systematic literature review (SLR) and network meta-analysis (NMA) of first-line therapies (1L) for locally advanced/metastatic urothelial carcinoma (la/mUC).

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Background: Standard of care (SOC) for 1L la/mUC is gemcitabine plus cisplatin (GC) or carboplatin (GCa), but the landscape is evolving with new therapies emerging. To compare outcomes of other approved/investigational 1L regimens with SOC in the context of recently published data on newer therapies, we updated a previously reported SLR/NMA of phase 2/3 randomized control trials. **Methods:** The SLR was conducted in line with PRISMA and NICE guidelines (01/2000-05/2020; updated 06/2020-06/2021). Three networks were formed: cisplatin (cis)-eligible/mixed eligibility; cis-ineligible (strict; studies including cis-ineligible patients only); and cis-ineligible (wide; expanded to also include study arms with an investigator's choice of carboplatin in KEYNOTE-361, IMvigor130, and DANUBE). Comparative efficacy and safety were assessed under a Bayesian framework. Overall survival (OS) and progression-free survival (PFS) with 1L la/mUC regimens vs SOC (GC/GCa) are reported. **Results:** Among 2,312 citations identified, 55 unique trials were selected for data extraction. Of these, the NMA included 11 studies in the cis-eligible/mixed, 6 in the cis-ineligible (strict), and 8 in the cis-ineligible (wide) network. The NMA excluded therapies that were not effective or adopted in clinical practice; 6 maintenance trials were excluded due to differences in design precluding comparisons. Median OS in the SOC arms was 13.2 mo (95% confidence interval [CI] 12.4-14.0) for cis-eligible/mixed, 9.7 mo (95% CI 6.7-12.8) for cis-ineligible (strict), and 12.0 mo (95% CI 10.4-13.5) for cis-ineligible (wide); median PFS was 6.6 mo (95% CI 6.3-6.9) for cis-eligible/mixed and 5.6 mo (95% CI 5.0-6.3) for both cis-ineligible strict and wide. OS and PFS were similar to SOC across therapies in each network: hazard ratios (HR) ranged 0.7-1.4 for OS for cis-eligible/mixed, 0.9-1.4 for cis-ineligible (strict), and 0.8-1.4 for cis-ineligible (wide) (Table); HR for PFS ranged 0.5-1.6 for cis-eligible/mixed and 0.8-1.1 for both cis-ineligible strict and wide networks; all credible intervals (CrI) crossed or were close to 1. **Conclusions:** In this updated SLR/NMA, survival outcomes were similar and remained poor among established and emerging 1L la/mUC therapies, despite inclusion of recent trial data. This further highlights the unmet need in this population. Research Sponsor: Seagen Inc.

HR for OS vs SOC (cis-ineligible).

HR (95% CrI)	Cis-ineligible (strict)	Cis-ineligible (wide*)
Durvalumab + Tremelimumab	0.9 (0.7, 1.1)	NA
Durvalumab	0.9 (0.7, 1.2)	NA
Vinflunine + Gemcitabine	1.1 (0.6, 1.9)	1.1 (0.6, 1.9)
Oxaliplatin + Gemcitabine	1.4 (0.9, 2.3)	1.4 (0.9, 2.3)
Pembrolizumab	NA	0.8 (0.7, 1.1)
Pembrolizumab + GCa	NA	0.8 (0.7, 1.1)
Atezolizumab	NA	1.0 (0.8, 1.2)
Atezolizumab + GCa	NA	0.9 (0.7, 1.1)

*Includes KEYNOTE-361, IMvigor130, DANUBE. Results represent all-comers PD-1/L1 expressor status.

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Urothelial carcinoma with sarcomatoid variant: A preliminary study of clinical and pathological features.

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Background: Muscle-invasive urothelial carcinoma (UC) with sarcomatoid variant (SV) (SV-UC) occurs in 0.1-0.3% of UC cases, and has been related with worse prognosis. Due to rarity of SV-UC, there are still limited evidences about the predictive role of sarcomatoid differentiation and no agents has been tested for SV-UC. We aim to investigate clinical and pathology features of SV-UC in a high grade UC (HG-UC) patients (pts) cohort. **Methods:** A retrospective analysis was performed on pts with HG-UC referring to our center between December 2012 and June 2021. Pts were reviewed for availability of histological tumor samples to evaluate the presence of SV. The expression of PD-L1 was evaluated in SV-UC sample by immunohistochemistry (IHC) using Ventana (SP263) assay. An IHC expression $>$ 5% was considered positive. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method and compared with the log-rank test. The Chi-Square test, t-test or Wilcoxon-Mann-Whitney test were used to assess difference between the groups as appropriate. **Results:** A cohort of 73 HG-UC pts were analyzed and a total of 6 SV-UC has been identified (8.2%). Two cases (2.7%) presented both SV and rhabdoid features. The median age at diagnosis was 69 years (54-81). SV-UC occurs equally in male and female (50%) vs 9% of affected female in HG-UC group ($p = 0.02$). Of four patients experiencing a metastatic disease (67%), two were metastatic at diagnosis (33%). One patient had an upper tract UC (17%), while remaining samples originated from bladder. Of note, in 4/6 of pts (67%) a squamous histology was reported (vs 10.5% in HG-UC group; $p = 0.1$). SV was found in $>$ 30% of tissue sample in 4/6 cases, 15% in one case, undefined in the remaining one. The PD-L1 expression in SV-UC tissues was $>$ 50% in 5/6 of cases (83%), negative in the remaining one ($<$ 5%). All pts in SV-UC group had advanced stage of desease: 4/6 had pT3 stage (67%), 2/6 had pT4 stage (33%) and 4/6 had positive loco-regional lymph nodes. All SV-UC pts had local recurrence. Four pts with metastatic desease were treated with chemotherapy, and 3 received also immunotherapy. The majority of treated pts (2/3) achieved progression as best first line response (22% in HG-UC). With a median follow up of 33 months (range 2-110), median PFS was 1.3 and 6.3 months (HR 0.51, 95%CI 0.11-2.17, P = 0.36) and median OS was 8.9 vs 20.3 months in SV-UC and HG-UC group, respectively (HR 0.51, 95%CI 0.11-2.17, P = 0.36). **Conclusions:** This analysis explored incidence and clinico-pathologic features of SV in pts with HG-UC, identifying an often underestimated subpopulation. Compared to HG-UC, SV-UC appears to be associated with lower M:F ratio, squamous histology, advanced disease and higher PD-L1 expression. Our initial results confirmed an association with shorter PFS and OS. The major limitation of our series is the small number of cases, a larger study is already planned. Research Sponsor: None.

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Heterogeneity of BCG unresponsive bladder cancer clinical trials limits patients' access to novel therapeutics.

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Background: Effective therapies for patients with non-muscle invasive bladder cancer that recurs or progresses after Bacille Calmette-Guérin (BCG) are lacking. This unmet need is the focus of many drug development efforts, reflected in many completed/ongoing/planned clinical trials for patients with BCG unresponsive bladder cancer. Though BCG unresponsive criteria are well defined, enrollment criteria are variable such that, even at centers with several open trials in this space, a given patient with BCG unresponsive bladder cancer might not qualify for any. To understand the scope of this dilemma, we systematically analyzed enrollment criteria for all BCG unresponsive protocols registered on ClinicalTrials.gov to quantify heterogeneity in enrollment criteria and to determine what proportion of trials were inclusive to patients meeting U.S. Food and Drug Administration (FDA) BCG unresponsive criteria. **Methods:** The ClinicalTrials.gov search tool was queried for relevant trials using the terms 'bladder cancer' 'non-muscle invasive bladder cancer' and 'BCG'. Previously published review articles were cross-referenced to ensure that search results were comprehensive. Inclusion and exclusion criteria for the resulting 28 protocols pertaining to distinct categories such as performance status, laboratory parameters, co-morbidities, active medications, and prior therapies were recorded. Based on enrollment criteria, the trial was assessed to fully inclusive or not to patients considered to be BCG unresponsive by the 2018 FDA criteria. **Results:** Of 28 trials, 15 (54%) had inclusion/exclusion criteria that were consistent with (inclusive of patients that met) the BCG unresponsive bladder cancer definition. 13 (48%) of 27 trials that specified performance status excluded patients with ECOG $>$ 2 (or KPS equivalent). The most common disease specific exclusion for patients with BCG unresponsive bladder cancer was a requirement for stage Tis (carcinoma *in situ*, CIS), which pertained to 5 (18%) of trials. **Conclusions:** Enrollment criteria for patients with BCG unresponsive bladder cancer are highly variable. Nearly half of patients who meet stringent criteria for this disease state do not qualify for clinical trials in this area. For patients who desire to enroll in clinical trials, this restricts access to novel agents. For bladder cancer treating physicians and regulatory bodies, this also hinders comparisons across agents. Research Sponsor: Ohio State University Comprehensive Cancer Center.

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Long-term follow-up of intravesical gemcitabine and docetaxel as rescue therapy for nonmuscle-invasive bladder cancer.

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Background: Intravesical bacillus Calmette-Guérin (BCG) is the first-line treatment for high-risk nonmuscle invasive bladder cancer (NMIBC). Unfortunately, disease recurrence/progression is common and associated with increased risk of death from bladder cancer. While radical cystectomy remains the preferred treatment for BCG unresponsive NMIBC, many patients are either unwilling or unfit to undergo surgery. Previous retrospective studies have demonstrated the efficacy of intravesical gemcitabine and docetaxel (Gem/Doce) for treating NMIBC after BCG failure. However, the long-term outcomes of this cohort are unknown. We report 5-year survival outcomes of patients treated with intravesical Gem/Doce after BCG failure. **Methods:** We retrospectively identified patients at our institution who were treated with Gem/Doce for high-risk NMIBC after BCG failure between 2009 and 2017. Patients received six weekly intravesical Gem/Doce instillations. Initial responders received monthly maintenance instillations for 2 years. Surveillance was performed according to American Urological Association guidelines. Survival time was measured from start of Gem/Doce induction. Outcomes included high-grade recurrence-free survival (HG-RFS), progression-free survival (PFS), cystectomy-free survival (CFS), cancer-specific survival (CSS) and overall survival (OS). Recurrence was defined as pathologically confirmed tumor relapse in the bladder or prostatic urethra. Progression was defined as recurrence of disease with stage T2 or greater, cystectomy or death due to bladder cancer. Survival probabilities were calculated with the Kaplan-Meier method. **Results:** A total of 97 patients with a median age of 73 years were treated with Gem/Doce after BCG failure. Median follow-up was 49 months. BCG failure was further stratified as BCG unresponsive (35%), BCG relapsing (38%), BCG intolerant (11%) or unspecified (16%). 71% and 21% of patients had carcinoma in-situ and high-grade T1 disease, respectively. Complete response at initial surveillance was 74% and median duration of response was 26 months. Overall HG-RFS at 1, 2 and 5 years was 60%, 51% and 31%, respectively. HG-RFS was similar among BCG unresponsive patients and the overall cohort (see table). During follow-up, 18 patients (19%) underwent radical cystectomy and 28 patients (29%) experienced disease progression. PFS, CFS, CSS and OS at 5 years was 68%, 75%, 91% and 64%, respectively. **Conclusions:** Intravesical Gem/Doce for high-risk NMIBC after BCG failure offers long-term efficacy and substantial durability of response with a high likelihood of bladder preservation at five years after induction. Future prospective trials assessing Gem/Doce are warranted. Research Sponsor: John & Carol Walter Family Foundation, Carver College of Medicine.

Survival Outcome	1 Year	2 Years	5 Years
Overall HG-RFS	60%	51%	31%
BCG unresponsive HG-RFS	67%	53%	33%
PFS	86%	79%	68%
CFS	89%	86%	75%
CSS	99%	97%	91%
OS	96%	87%	64%

Cost effectiveness of newly approved second/third-line agents in metastatic urothelial carcinoma (mUC).

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Background: Over the past years, the treatment landscape of platinum-refractory mUC has drastically changed with the advent of immunotherapy. More recently, several new agents including enfortumab, erdafitinib, and sacituzumab have received F.D.A. approval for the treatment of platinum-refractory mUC. It is unclear if these newly approved therapies may be cost prohibitive for patients and/or hospitals/clinics compared to the recommended NCCN category 1 second-line agent, pembrolizumab. **Methods:** Using acquisition costs from our home institution's cancer center pharmacy department, we calculated the total cost of treatment for each agent. We used phase II clinical trial data to determine the median duration of treatment for each therapy. For weight-based therapies, we used 70 kg as the weight for an average human adult. **Results:** The three newly approved therapies for mUC have total acquisition costs in descending order as follows: enfortumab vedotin ($153,697.50), edafitinib ($131,642.62), and sacituzumab govitecan ($63,198.07). Enfortumab and sacituzumab likely have higher total costs given both therapies require infusion center use for administration, and are associated with infusion center administration fees. In comparison, pembrolizumab (standard of care per NCCN guidelines) has a total acquisition cost of $51,343.60. **Conclusions:** Based off median duration of treatment, pembrolizumab has the lowest total acquisition cost compared to the three newly approved therapies for mUC. Further statistical analysis of this data set is ongoing. In particular, analysis will include out-of-pocket costs for patients as well as quality-adjusted life years (QALY). Research Sponsor: None.

Cost effectiveness analysis of 2nd/3rd line agents in mUC.

Drug	Unit cost (USD)[1]	Average length/ cycles	Cost per cycle	Infusion Center Cost	Total cost (USD)	Survival benefit (PFS, months; OS, months)
Erdafitinib	$24,838.23 for 28-day supply of 9 mg	5.3 months was median duration of treatment in trial	$24,838.23 for 28-day supply of 9 mg	No	$131,642.62	PFS: 5.55 (phase II data, Loriot et al. NEJM 2019) OS: 13.8
Enfortumab vedotin	$2,277 per 20 mg vial $3,415.50 per 30 mg vial	5.0 months was median duration of treatment per trial	$30,739.50 per 28 day cycle for 70-kg person	Yes	$153,697.50	PFS: 5.55 versus 3.71 with chemotherapy (phase III data, Powles et al. NEJM 2021) OS: 12.88
Sacituzumab govitecan	$2,135.07 per single-use 180 mg vial	3.7 months was median duration of treatment per trial	$ 17,080.56 per 21-day cycle for 70 kg-person	Yes	$63,198.07	PFS: 5.4 (phase II data, Tagawa et al. JCO. 2021) OS: 10.9
Pembrolizumab (comparator)	$5,134.36 for 100 mg vial	3.6 months was median duration of treatment per trial	$10,268.72 per 21-day cycle (200 mg per cycle)	Yes	$51,343.60	PFS: 2.1 (phase II data, Bellmunt et al. NEJM 2017) OS: 10.3

Pricing per UC Irvine Health acquisition costs as of 9/22/2021.

575 **Poster Session**

Five-year survival comparison of different treatment modalities for muscle invasive urothelial carcinoma, squamous cell carcinoma and adenocarcinoma of the bladder: An analysis of the National Cancer Database.

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Background: Localized muscle invasive bladder cancer carries a significant recurrence and mortality rate. The purpose of this study was to compare 5-year overall survival (OS) of neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC), RC alone, bladder preserving chemoradiotherapy (BPCRT) and radiation alone (RT) on selected histologies. **Methods:** We sampled the National Cancer Database (NCDB) for bladder cancer patients diagnosed with AJCC 7th Stage 2 and 3 for urothelial carcinoma (UC) including variant histologies, squamous cell carcinoma (SCC) and adenocarcinoma (AC) from 2004-2018 with definitive intent treatment. 5-year Kaplan-Meier survival plots were utilized to assess survival differences amongst treatment modalities and stratified by selected histologies. Multivariate cox regression models were used to compare hazard ratios and logistic regression analysis was performed for covariate analysis. A p-value <0.05 was considered statistically significant. **Results:** A total of 20,629 patients met inclusion criteria. The average age was 69.51 + 11.02 years, 68% were male. UC represented 94.1% of selected histologies, followed by 4.6% SCC and 1.3% AC. For all combined histologies, 5-year OS for patients with NAC followed by RC was 58%, 48% for RC alone, 33% for BPCRT and 10% for RT alone. RC alone provided a longer OS in the SCC and AC groups, 48% and 47% respectively ($p<0.001$). NAC followed by RC showed superior OS in the UC group (58%, $p<0.001$), with OS decreasing to 43% in SCC and 44% in AC. BPCRT showed lower 5-year OS in all selected histologies when compared to NAC followed by RC and RC alone (33% in UC, 27% in SCC and 24% in AC group). In all selected histologies, RT showed the lowest 5-year OS (10% in UC, 8% in SCC and 17% in AC group; $p<0.001$). Furthermore, covariables associated with lower 5-year survival were male sex ($p<0.001$) and TNM Stage 3 ($p<0.001$). **Conclusions:** NAC followed by RC showed improved 5-year OS for UC. The benefit of NAC was marginal for SCC and AC histology. RC is better than BPCRT for all histologies. RT alone showed inferior 5-year OS for all histologies. Research Sponsor: None.

Treatment Patients N = 20629	Urothelial Carcinoma Histology N (%)	Squamous Cell Carcinoma Histology N (%)	Adenocarcinoma Histology N (%)	Odd Ratio (CI)	Hazard Ratio (CI)	p-value
NAC followed by RC	5117 (26.4)	104 (10.9)	40 (14.9)		1	-
RC Alone	8250 (42.5)	658 (69.2)	161 (59.9)		1.45 (1.38-1.52)	< 0.001
BPRCT	5806 (29.9)	156 (16.4)	62 (23.0)		2.02 (1.92-2.13)	< 0.001
RT Alone	236 (1.2)	33 (3.5)	6 (2.2)		5.21 (4.57-5.94)	< 0.001
Charlson Deyo Score (CDS = 0)		66.9% (n=13811)		1		-
CDS = 1		21.8% (n=4501)		1.87 (1.60 - 2.19)		< 0.001
CDS = 2		7.6% (n=1572)		1.24 (1.05 - 1.46)		<0.01
TNM Stage 2		82.8% (n=17076)		1		–
TNM Stage 3		17.2% (n=3553)		1.67 (1.55 - 1.81)		< 0.001

Recurrence patterns in bladder cancer patients with no residual disease (pT0N0) at radical cystectomy.

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Background: Bladder cancer patients can achieve no residual disease status at the time of radical cystectomy (RC) following transurethral resection (TURBT) alone (pT0) or neoadjuvant chemotherapy (NAC) (ypT0). This population has favorable survival potential, yet limited data is available on their oncological outcomes. We examined the recurrence patterns in these patients and the implications for post-operative surveillance. **Methods:** A retrospective review of our IRB-approved bladder cancer database identified patients who underwent RC between 2000 - 2019 and were found to have no residual disease (pT0N0). The primary outcome was recurrence-free survival (RFS). **Results:** A total of 234 patients with a median age of 67 years were included. NAC was used in 89 (38%) patients and 145 (62%) cases were rendered pT0 following TURBT alone. After a median follow up of 44 months, 6/145 (4%) pT0 patients and 10/89 (11.2%) ypT0 cases developed a recurrence. None of the pT0 patients with previous history of clinical Ta/Tis disease had a recurrence after RC. The median time to recurrence was 9 months. All but one of the recurrences in the ypT0 group were within 2 years of cystectomy, while half of the recurrences in the pT0 group occurred after 2 years. Patients with ypT0 had worse 2- and 5-year RFS compared to the pT0 group (85% and 84% vs. 99% and 95%, respectively; p=0.003). Variant histology was noted in 49 (21%) patients and the recurrence rate was higher in this subgroup compared to those with pure urothelial carcinoma (12.2% vs. 5.4%, p = 0.02). Lung metastasis and involvement of distant organs, while rare, was noted at similar rates in both groups (Table). On univariate Cox regression analysis of RFS, clinical T stage $>$ 3 (HR: 6.5, 95%CI: 2.4 – 17.3, p$<$0.001) and NAC (HR: 4.3, 95%CI: 1.5 – 12.5, p = 0.007) were associated with increased risk of recurrence. **Conclusions:** Most patients with pT0N0 pathology at the time of cystectomy are cured however metastasis can still develop up to 4 years after surgery. Patients achieving ypT0 after NAC exhibit worse prognosis and shorter times to recurrence, and closer follow-up may be considered. Research Sponsor: None.

Detailed recurrence data ordered by time to recurrence.

Surgery Date	Clinical Stage	Variant Histology	NAC	Time to Recurrence (months)	Recurrence Location
2018	T2	Sarcomatoid	GC	1.9	Lungs, Mediastinal, RP Nodes
2012	T2	Sarcomatoid	**None**	2.7	Lungs, Pelvic, RP Nodes
2013	T3	No	GC	4.8	Carcinomatosis
2010	T2	Neuroendocrine	GC	5	Liver
2013	T4	No	GC	5.4	Pelvic Nodule
2016	T3	No	GC	6.9	Rectum
2015	T1	No	**None**	7.7	Lungs
2017	T4	No	ddMVAC	9	Brain
2015	T4	Plasmacytoid/ Glandular	GC	9.1	Sigmoid Colon
2001	T1	No	**None**	11.8	Pelvic Nodule
2015	T2N1	No	GC	20.8	RP Nodes
2008	T3	Glandular	ddMVAC	24	Lungs
2011	T3	Signet cell/ Plasmacytoid	MVAC	34.4	Rectum
2011	T2	No	**None**	39.3	Lungs
2011	T1	No	**None**	43.3	Bone, Liver, Adrenal gland
2000	T2	No	**None**	49.9	Vaginal Wall

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Incidence and outcomes of nodal metastasis in clinically nonmuscle-invasive bladder cancer.

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Background: Radical cystectomy (RC) is recommended in NMIBC patients with high risk of progression or persistent disease despite intravesical therapy. The role and extent of lymphadenectomy is controversial and not universally performed in this population. The objective of this study is to evaluate the incidence and pattern of nodal metastasis in patients undergoing radical cystectomy for treatment of clinically non-muscle invasive bladder cancer. **Methods:** Prospectively collected data of patients who underwent RC and 'super-extended' LND with intent-to-cure for urothelial carcinoma of the bladder between 2002 and 2019 were examined. Inclusion criteria were(a) clinical stage Ta, Tis,or T1, (b) muscle present and not involved,(c) no prior diagnosis of T2 disease, (d) no prior neoadjuvant therapy, and (e) super-extended lymphadenectomy performed to level of IMA with mapping information available. Logistic regression analysis was used to evaluate for predictors of node metastasis. **Results:** A total of 223 patients met inclusion criteria with a median follow up of 8.2 years (IQR 4.1-10.7). Lymph node metastasis was identified in 8.1% (18/223) of the cohort. Nodal metastasis was present in 0 patients with cTis, 0 patients with cTa, and 11.6% (18/155) of patients with cT1 disease. Of the 18 patients with LNM in cT1 disease, 61% (11/18) had positive nodes below the common ileac vessel bifurcation, 6% (1/18) had positive nodes below the level of aortic bifurcation, and 33% (6/18) had distant metastasis to lymph nodes beyond aortic bifurcation. No skip metastasis were identified. After RC, 89% of cT1 with nodal metastasis had muscle invasive disease. On logistic regression analysis, presence of LVI on TURBT specimen was a significant predictor of LNM (OR 6.8, CI 2.2-20.9). Five-year RFS was 91%, 82%, and 61% in patients with pNMIBC, cNMIBC, and pMIBC, respectively. **Conclusions:** Routine lymph node dissection is necessary in patients undergoing RC for cT1 disease due to risk of upstaging and LNMs. Presence of LVI in TURBT specimen of cNMIBC is a predictor of nodal metastasis. In patients with nodal disease, metastasis beyond the limits of a standard lymph node template occurred in two-thirds of patients, however a standard pelvic node dissection would have identified all patients with node positive disease. Research Sponsor: None.

TPS578 **Trials in Progress Poster Session**

PATRIOT II: An ambispective, observational, multicenter, 2-cohort study of avelumab (Ave) first-line maintenance (1LM) in locally advanced/metastatic urothelial carcinoma (la/mUC) in the United States.

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Background: The randomized phase 3 JAVELIN Bladder 100 trial demonstrated overall and progression-free survival (OS and PFS) benefit with Ave 1LM for la/mUC not progressed with platinum-containing chemotherapy (PCT). PATRIOT II aims to understand real-world treatment (tx) patterns, patient-reported outcomes (PRO), and healthcare resource utilization (HCRU; eg, hospitalizations and emergency department visits) before and during Ave 1LM treatment. **Methods:** PATRIOT II is an ongoing, real-world, observational study in ≤25 US oncology centers with 1) an ambispective cohort of patients (pts) initiating PCT (n = 100), a subset of whom may continue to Ave 1LM and 2) a retrospective cohort initiated on Ave 1LM (n = 150). Sample size assumes noninferiority in HCRU and PRO pre and post 1LM initiation using paired t-tests with effect size of ≤0.3 as noninferior: ≥71 patients continuing to 1LM. In the ambispective cohort, pts with histologically confirmed la/mUC newly initiating 1L PCT are enrolled. While pts are receiving PCT and 1LM (for those who receive it), data will be collected on disease characteristics, response to tx, survival, adverse events (AEs), and HCRU for ≤52 wks after study initiation. PROs are captured using Rand SF-36 question 1, FACT Bladder Symptom Inventory – 18 and Cancer Treatment Satisfaction Questionnaire. Primary outcomes include OS and PFS from both PCT and 1LM initiation; secondary outcomes are changes in PROs and HCRU from PCT to 1LM. Analysis will be conducted at following time points: 1) baseline characteristics after full enrollment; 2) 6 months after study initiation to assess tx changes and rationale, OS, PFS, HCRU, and PRO changes from baseline; 3) at study conclusion (wk 52 after study initiation). In the retrospective cohort, pts with la/mUC who initiated Ave 1LM are enrolled. Chart data encompasses PCT and 1LM periods. Disease characteristics, response to tx, survival, AEs, and HCRU are collected. Primary outcomes are OS and PFS from initiation of PCT and 1LM start. Secondary outcomes are changes in HCRU before and after 1LM. Analysis will be conducted at following time points: 1) baseline characteristics after full enrollment, PCT, and response to tx; 2) 6 months after study initiation to assess tx changes since baseline, including dose changes, tx discontinuation/change rationale, survival rates (censoring for differential duration of follow-up), and HCRU outcomes; 3) at study conclusion to analyze endpoints up to wk 52 following study initiation. Analyses for both cohorts include Kaplan-Meier and Cox regression for time-to-event endpoints and paired t-tests for pre/post 1LM. Enrollment commenced in June 2021. 5 and 18 pts are enrolled to date in the ambispective and retrospective cohorts, respectively, from 6 of 11 activated sites. Initial results are anticipated in May 2022. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), Pharmaceutical/Biotech Company.

TPS579 **Trials in Progress Poster Session**

A phase 3, randomized, open-label, multicenter, global study of the efficacy and safety of durvalumab (D) + tremelimumab (T) + enfortumab vedotin (EV) or D + EV for neoadjuvant treatment in cisplatin-ineligible muscle-invasive bladder cancer (MIBC) (VOLGA).

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Background: The standard management of MIBC involves neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and pelvic lymph node dissection. Approximately 40% of patients with MIBC are cisplatin ineligible, the standard of care (SoC) for these patients is to proceed directly to cystectomy as there are no effective or approved neoadjuvant therapies in this setting. Only nivolumab has been approved as adjuvant treatment for patients who are at high risk of recurrence after radical resection. Given this, there remains an unmet need. D (anti–PD-L1 antibody) +T (anti–CTLA-4 antibody) have demonstrated a manageable safety profile with clinical activity in metastatic urothelial carcinoma and in a phase 2 neoadjuvant trial, D+T showed anti-tumor activity, including meaningful pathologic complete responses (pCR), in cisplatin-ineligible MIBC with high-risk features. Targeted cytotoxic antibody drug conjugates (ADCs) are known to have the potential to induce immunogenic tumor cell death, which promotes activation and recruitment of immune cells. EV is a vedotin ADC comprising an antibody against Nectin-4 linked to a microtubule-disrupting agent MMAE that has demonstrated efficacy in, and is approved for, advanced urothelial cancer. Thus, we hypothesize that EV in combination with PD-L1 inhibition, with or without CTLA-4 inhibition, may improve outcomes in patients with MIBC by downstaging of disease before cystectomy and that adjuvant therapy with D or D+T may further improve time to disease relapse. **Methods:** VOLGA (NCT04960709) is a phase 3, randomized, open-label, multicenter, international trial that will enroll ~830 patients with MIBC. Eligible patients include those aged ^{3}18 years with histologically or cytologically documented MIBC (transitional and mixed transitional cell histology), who are cisplatin ineligible and with a clinical stage of T2-4aN0-N1M0. Patients will be randomized to 3 arms to receive 3 cycles of neoadjuvant therapy Q3W as follows: (Arm 1) D (1500 mg day 1) +T (75 mg day 1) +EV (1.25 mg/kg Days 1 & 8); (Arm 2) D (1500 mg day 1) +EV (1.25 mg/kg Days 1 & 8); or (Arm 3) no neoadjuvant treatment (SoC). A safety run-in study is included. Following radical cystectomy, patients will then receive: (Arm 1) 1 cycle of T on Day 1 plus 9 cycles of D Q4W; (Arm 2) 9 cycles of D Q4W; or (Arm 3) either no adjuvant treatment (observation only) or adjuvant nivolumab in high-risk patients where available and approved (planned amendment). The dual primary endpoints are pCR and event-free survival. Secondary endpoints include overall survival, disease-free survival, pathologic downstaging rate to $<$ pT2, disease-specific survival, quality of life, immunogenicity, and pharmacokinetics. The study is actively enrolling. Clinical trial information: NCT04960709. Research Sponsor: AstraZeneca.

TPS580 **Trials in Progress Poster Session**

Adjuvant infigratinib as targeted therapy for patients with muscle-invasive urothelial carcinoma harboring susceptible *FGFR3* genetic alterations: A randomized, double-blind, placebo-controlled, phase 3 trial (PROOF 302).

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Background: Radical surgery is the mainstay of treatment for muscle-invasive upper tract urothelial cancer (UTUC) and urothelial bladder cancer (UBC). However, even when surgery is combined with cisplatin-based (neo)adjuvant chemotherapy, recurrence rates are high. Many patients (pts) are ineligible for, do not respond to, or refuse cisplatin-based chemotherapy because of toxicity concerns. Fibroblast growth factor receptor 3 (*FGFR3*) genetic alterations occur in 21–38% of muscle-invasive UTUC, and in approx. 20% of invasive UBC. Infigratinib (BGJ398) is an ATP-competitive FGFR1–3 selective oral tyrosine kinase inhibitor that has clinical activity and tolerability in pts with advanced/metastatic urothelial carcinoma (UC) harboring susceptible *FGFR3* alterations. PROOF 302 was designed to investigate the efficacy and safety of adjuvant infigratinib in pts with high-risk, muscle-invasive UC (85% UTUC) and susceptible *FGFR3* alterations. **Methods:** PROOF 302 is a global, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial (NCT04197986). Eligible pts have high-risk, muscle-invasive UTUC (85%) or UBC (15%) with susceptible *FGFR3* alterations (mutations, gene fusions or rearrangements) confirmed by FoundationOne CDx test, and are ≤120 days following nephroureterectomy, distal ureterectomy, or cystectomy. The study protocol was amended to include pts with carcinoma *in situ* at surgical margins and those who refuse cisplatin-based chemotherapy (in addition to pts allowed to enroll if ineligible for perioperative cisplatin-based chemotherapy). Eligible pts are M0 and have either disease stage ≥ypT2 and/or yN+ after cisplatin-based neoadjuvant chemotherapy or ≥pT2 pN0–2 or pN+ (UTUC); and ≥pT3 or pN+ (UBC) if not treated with cisplatin-based neoadjuvant chemotherapy. Pts are randomized 1:1 to receive oral infigratinib 125 mg or placebo QD on days 1–21 of a 28-day cycle for up to 52 weeks (13 cycles) or until recurrence, unacceptable toxicity, or death. Primary endpoint: centrally reviewed disease-free survival (DFS) analyzed via stratified log-rank test and Cox model (hazard ratio). Secondary endpoints: investigator-reviewed DFS, metastasis-free survival, overall survival, safety/tolerability. Exploratory endpoints: quality of life, pharmacokinetics, determination of the prevalence of genomic alterations and correlation with features of UC, genomic and proteomic assessment of tumor tissue and cell-free DNA samples from baseline and at recurrence to identify the predictive/prognostic value of biomarkers. PROOF 302 is actively enrolling as of Sep 2021. A second Data Monitoring Committee meeting is planned for Dec 2021. The last pt is expected to complete treatment in 2024. Clinical trial information: NCT04197986. Research Sponsor: QED Therapeutics Inc.

TPS581 **Trials in Progress Poster Session**

TROPHY-U-01 cohort 4: Sacituzumab govitecan (SG) in combination with cisplatin (Cis) in platinum (PLT)-naïve patients (pts) with metastatic urothelial cancer (mUC).

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Background: Cis-based combination chemotherapy regimens with gemcitabine or methotrexate, vinblastine, and doxorubicin are commonly used as initial treatment for mUC. However, only a fraction of pts maintain a durable response. Alternative Cis-based combinations with improved efficacy while maintaining tolerability are needed. SG is an antibody-drug conjugate (ADC) composed of an anti-trophoblast cell-surface antigen-2 (Trop-2) antibody coupled to SN-38 (a topoisomerase-I inhibitor) via a proprietary hydrolyzable linker. In vitro/in vivo urinary bladder cancer models suggest that the combination of SG and Cis resulted in additive antitumor activity over either agent alone (data on file). In the phase 2 registrational TROPHY-U-01 study, SG monotherapy resulted in a 27% objective response rate (ORR) and a median overall survival (OS) of 10.9 months with a manageable, mostly non–Cis-overlapping toxicity profile in heavily pretreated pts with mUC (Tagawa et al, *J Clin Oncol*. 2021). These results led to accelerated approval of SG by the FDA in 2021 for pts with locally advanced or mUC who previously received PLT-containing chemotherapy and a checkpoint inhibitor. We hypothesized that SG and Cis in combination may improve efficacy/safety over available first-line mUC regimens. TROPHY-U-01 Cohort 4 study will evaluate the safety, tolerability, and clinical activity of this novel combination. **Methods:** TROPHY-U-01 (NCT03547973) is a multicohort, open-label, global phase 2 trial. Cohort 4 will evaluate combination SG and Cis in PLT-naive pts with mUC or unresectable locally advanced disease. Key eligibility requirements include Eastern Cooperative Oncology Group performance status 0–1; no prior anticancer monoclonal antibody or ADC therapy within 4 weeks of study drug initiation; no history of active interstitial lung disease or noninfectious pneumonitis; adequate hematologic, hepatic, and renal function. Pts will be treated with Cis at 70 mg/m^2 on day 1 of a 21-day cycle (if creatinine clearance [CrCl] $\geq$60 mL/min) or at a split dose of Cis at 35 mg/m^2 on days 1 and 8 of a 21-day cycle (if CrCl 50-59 mL/min) followed by SG (5, 7.5, or 10 mg/kg) on days 1 and 8 of a 21-day cycle. The recommended phase 2 dose will be the dose in which $\leq$30% dose-limiting toxicities are noted in cycle 1. Combination therapy will continue for up to 6 cycles, followed by SG and avelumab maintenance given until progression. Prophylactic granulocyte colony-stimulating factor is not allowed in cycle 1 of the safety lead-in phase. Primary endpoint is ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints include progression-free survival, duration of response, and clinical benefit rate per BICR and investigator assessment. OS and safety will be assessed. Enrollment is ongoing; ~60 pts expected across ~30 sites in North America and Europe. Clinical trial information: NCT03547973. Research Sponsor: Gilead Sciences, Inc.

TPS582 **Trials in Progress Poster Session**

TROPiCS-04: Study of sacituzumab govitecan (SG) in patients (pts) with locally advanced (LA) unresectable or metastatic urothelial cancer (mUC) that has progressed after prior platinum (PLT) and checkpoint inhibitor (CPI) therapy.

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Background: Treatment options are limited for pts with LA unresectable or mUC who progress after prior PLT-based and CPI therapies. SG is an antibody-drug conjugate (ADC) composed of an anti-trophoblast cell surface antigen 2 (Trop-2) antibody coupled to SN-38 (a topoisomerase-I inhibitor) via a proprietary hydrolyzable linker. In the phase 2 registrational study TROPHY-U-01 (NCT03547973), SG demonstrated an objective response rate (ORR) of 27% and median overall survival (OS) of 10.9 months in pts with mUC who progressed after prior PLT-based and CPI therapies (n = 113; median, 3 prior lines of therapy; 84% with ≥1 Bellmunt risk factors; Tagawa et al, *J Clin Oncol.* 2021). These results compared favorably with historic data for single-agent chemotherapy (ORR, ~18%; OS, 9 months; Powles et al. *J Clin Oncol.* 2021) and led to accelerated approval of SG by the US Food and Drug Administration for pts with LA or mUC who previously received a PLT-containing chemotherapy and CPI. The phase 3 TROPiCS-04 trial has been initiated to confirm these findings. **Methods:** TROPiCS-04 (NCT04527991) is a global, multicenter, open-label, randomized, controlled trial in pts with LA unresectable or mUC who progressed after prior PLT-based and CPI therapies. Key eligibility requirements include Eastern Cooperative Oncology Group performance status 0-1; no prior CPI or ADC therapy within 4 weeks of study drug initiation; no history of active interstitial lung disease or non-infectious pneumonitis; and adequate hematologic, hepatic, and renal function. Pts will be randomly assigned 1:1 to receive SG 10 mg/kg intravenously (IV) on days 1 and 8 of 21-day cycles or single-agent treatment of physician's choice (paclitaxel 175 mg/m^2, docetaxel 75 mg/m^2, or vinflunine 320 mg/m^2 IV on day 1 of 21-day cycles) until progressive disease, unacceptable toxicity, or withdrawal of consent. Treatment beyond progressive disease may be permitted in pts deemed to be receiving clinical benefit per investigator assessment. Approximately 600 pts will be enrolled across ~280 sites in 3 regions (North America, Europe, and Asia-Pacific) to provide 90% power on the primary endpoint of OS. Secondary endpoints include progression-free survival, ORR, clinical benefit rate, duration of response (all per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review and investigator assessment), safety, and quality of life. Study enrollment started in January 2021 and is ongoing with pts currently enrolled at 30 sites across all 3 regions. Clinical trial information: NCT04527991. Research Sponsor: Gilead Sciences, Inc.

TPS583

Trials in Progress Poster Session

Abstract Withdrawn

TPS584 **Trials in Progress Poster Session**

A phase 2, multiarm study of anti-CD47 antibody, magrolimab, in combination with docetaxel in patients with locally advanced or metastatic solid tumors.

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Background: Patients with solid tumors who progress on standard chemotherapy and/or immune checkpoint inhibitors have limited efficacy with existing standard-of-care chemotherapy options (objective response rates [ORRs] ~10%). These patients have a significant unmet medical need. Novel agents that can safely enhance treatment efficacy are urgently needed. Magrolimab is a first-in-class monoclonal antibody that blocks the macrophage inhibitory immune checkpoint CD47, a "do not eat me" signal overexpressed on tumor cells. Preclinical studies provide compelling evidence that magrolimab triggers phagocytosis and eliminates cancer cells from human solid tumors and hematologic malignancies. Magrolimab has demonstrated clinical activity in both hematologic and solid tumor malignancies. Chemotherapeutic agents, including taxanes, enhance prophagocytic signals on tumor cells, leading to synergistic antitumor activity when combined with magrolimab. This study (NCT04827576) is evaluating the safety, tolerability, and efficacy of magrolimab with docetaxel in relapsed/refractory (R/R) metastatic urothelial cancer (mUC), non-small-cell lung cancer (mNSCLC), and small-cell lung cancer (mSCLC). **Methods:** This Phase 2, open-label, multi-arm study (NCT04827576) consists of a safety run-in cohort and a Phase 2 cohort. Eligible patients are ≥18 years old with chemotherapy- and/or immunotherapy-refractory mUC, mNSCLC, or mSCLC. Magrolimab is administered intravenously (IV) with an initial 1-mg/kg priming dose to mitigate on-target anemia, followed by a 30-mg/kg dose during cycle 1 (cycles are 21 days) in the safety run-in to identify any dose-limiting toxicities (DLTs) and determine a recommended Phase 2 dose (RP2D). De-escalation may occur for DLTs per protocol. In Phase 2, following the priming dose on day 1, the highest acceptable dose of magrolimab will be administered on days 8 and 15 of cycle 1; days 1, 8, and 15 of cycle 2; and day 1 for cycles 3 and beyond. Docetaxel 75 mg/m^2 is administered IV on day 1 of each cycle for all study participants. Patients may continue treatment until unacceptable toxicity, progressive disease by RECIST 1.1, or patient/investigator choice to discontinue. The primary endpoints are incidence of adverse events (safety and Phase 2 cohorts) and ORR (Phase 2). Secondary endpoints (Phase 2) are progression-free survival, duration of response, and overall survival. Exploratory endpoints are to evaluate the pharmacodynamic, mechanism of action, and/or therapeutic response of biomarkers in blood and tumor biopsy samples and to explore biomarkers that may predict response to therapy. Enrollment began in August 2021. Planned enrollment is approximately 116 patients, and as of October 1, 2021 recruitment is ongoing. Clinical trial information: NCT04827576. Research Sponsor: Gilead Sciences, Inc.

TPS585 **Trials in Progress Poster Session**

Trial in progress: A phase 2, randomized, open-label study of trilaciclib with first-line, platinum-based chemotherapy and avelumab maintenance in untreated patients with locally advanced or metastatic urothelial carcinoma (PRESERVE 3).

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Background: Trilaciclib is an intravenous (IV) CDK4/6 inhibitor that has been shown to help protect hematopoietic stem and progenitor cells from chemotherapy (CT)-induced damage (myeloprotection) via transient cell cycle arrest. Trilaciclib is approved in the US to decrease the incidence of CT-induced myelosuppression (CIM) in adult patients with extensive-stage small cell lung cancer receiving certain treatment regimens. An exploratory phase 2 study (NCT02978716) in patients with triple-negative breast cancer showed improved overall survival (OS) in patients receiving trilaciclib prior to CT vs CT alone, regardless of PD-L1 expression. The aim of this exploratory, randomized, open-label, multicenter, phase 2 trial (PRESERVE 3; NCT04887831) is to assess whether trilaciclib administered with standard-of-care platinum-based CT and avelumab maintenance can improve antitumor efficacy and reduce CIM versus CT and avelumab without trilaciclib, in patients with locally advanced or metastatic urothelial carcinoma (mUC). **Methods:** Adult patients with measurable disease per RECIST v1.1, no prior systemic treatment for mUC, and ECOG performance status ≤2 will be randomized 1:1 to receive gemcitabine 1000 mg/m^2 plus cisplatin 70 mg/m^2 or carboplatin area under the curve 4.5 (± trilaciclib 240 mg/m^2 IV over 30 minutes, ≤4 hours prior to CT) in 21-day cycles. Patients will receive 4–6 cycles of CT. Those without progressive disease per RECIST v1.1 can receive avelumab 800 mg maintenance therapy (± trilaciclib) in 14-day cycles until disease progression, unacceptable toxicity, investigator/patient decision, or end of trial. Patients will be followed for survival. The sample size was calculated to support the primary endpoint of progression-free survival (PFS), using a stratified log-rank test accounting for two stratification factors (visceral metastasis and platinum agent [cisplatin/carboplatin]). 63 PFS events will be required to achieve 77% power to detect a hazard ratio of 0.6 with a 2-sided significance of 0.2, corresponding to a median PFS of 11.7 months for the trilaciclib arm. Assuming a 10-month enrollment period, final PFS analysis approximately 22 months after the first randomization, and 5% loss to follow-up, 90 patients are required for randomization. PFS will be analyzed in the intention-to-treat population. Secondary endpoints include objective response rate, disease control rate, PFS during maintenance, OS, multilineage myeloprotective effects, and safety/tolerability. Exploratory endpoints will assess pharmacodynamic parameters, including those related to immune-based mechanisms, and efficacy by CDK4/6-dependence. Enrollment opened in June 2021. As of September 29, 2021, 8 sites are open, and 1 patient randomized. Clinical trial information: NCT04887831. Research Sponsor: G1 Therapeutics, Inc. Avelumab was provided by Pfizer as part of an alliance between Pfizer and the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

TPS586 **Trials in Progress Poster Session**

SGNTUC-019: Phase 2 basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations—Urothelial cancer cohort (trial in progress).

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Background: Tucatinib, a highly selective HER2-directed tyrosine kinase inhibitor approved in multiple regions for HER2+ metastatic breast cancer, is being investigated as a novel therapy for metastatic colorectal cancer, gastric cancer, and other GI tumors. In xenograft models of HER2+ and HER2-mutated tumors, dual targeting of HER2 with tucatinib and trastuzumab showed superior activity to either alone (Kulukian 2020; Peterson 2020). Despite development of several new therapies for metastatic urothelial cancer, most patients do not respond to subsequent therapies, and majority of patients succumb to the disease, highlighting the need for additional therapeutic approaches. Given 20%-30% of metastatic urothelial cancers have molecular alterations of the ErbB family, tucatinib + trastuzumab warrants further evaluation. SGNTUC-019 (NCT04579380) is a multi-cohort, open-label, international Phase 2 study evaluating tucatinib + trastuzumab in patients with previously treated solid tumors displaying HER2+ or HER2-mutated solid tumors, including a cohort with locally advanced or metastatic urothelial cancer (UC). **Methods:** Eligible patients must have HER2+ or HER2-mutated locally advanced or metastatic solid tumors, with progression on or after the last systemic therapy for advanced disease. Additionally, patients must have an ECOG PS $\leq$1, adequate hepatic, hematologic, renal, and cardiac function, and no prior exposure to HER2-directed therapy in the UC cohort. For eligibility, HER2 alterations can be demonstrated by HER2 overexpression/amplification in tumor tissue by prior IHC/ISH, or by HER2 amplification/mutation in prior or pre-screening NGS assay of ctDNA or prior tissue NGS assay. The HER2 overexpression/amplification UC cohort will enroll 12 response-evaluable patients per RECIST 1.1. If $\geq$2 responses are observed, the cohort will be expanded to 30. Patients with HER2-mutated UC will be enrolled into a cohort of 30 patients with HER2-mutated solid tumors (except breast and non-squamous non-small cell lung cancers). The primary objective is antitumor activity, with confirmed ORR as the primary endpoint, and disease control rate, duration of response, PFS, and OS as secondary efficacy endpoints. Patients will receive tucatinib 300 mg orally twice daily and trastuzumab 8 mg/kg intravenous on Cycle 1 Day 1 and 6 mg/kg q21 days from Cycle 2 Day 1. Disease assessments per RECIST 1.1 will occur q6 weeks for 24 weeks, then q12 weeks. Trough concentrations of tucatinib will be evaluated in Cycles 2-6, with a peak concentration sampled in Cycle 3. Quality of life will be evaluated q2 cycle using EQ-5D-5L. Sites are currently enrolling within the US, EU, and Asia Pacific. Clinical trial information: NCT04579380. Research Sponsor: Seagen Inc.

TPS587 **Trials in Progress Poster Session**

Study EV-103 cohort L: Evaluating perioperative enfortumab vedotin monotherapy in cis-ineligible muscle invasive bladder cancer (MIBC) (trial in progress).

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Background: The current standard of care for patients (pts) with newly diagnosed MIBC is neoadjuvant cisplatin (cis)-based chemotherapy followed by radical cystectomy and pelvic lymph node dissection (RC+PLND). For the 20-50% pts who are cis-ineligible, the current standard of care is RC+PLND alone (Galsky *Future Oncol* 2021). Adjuvant therapy is currently recommended for cis-ineligible patients with high-risk features at cystectomy. Due to the high rates of recurrence in cis-ineligible pts with RC+PLND alone, there is a need to develop new therapies in this setting. Enfortumab vedotin (EV), an antibody-drug conjugate, delivers the microtubule-disrupting agent monomethyl auristatin E to cells expressing Nectin-4, which is highly expressed in urothelial cancer. In EV-301, a phase 3 study, EV showed an overall survival (OS) benefit vs chemotherapy in pts with locally advanced (la) or metastatic urothelial carcinoma (mUC) who had previously received platinum-based therapy and a PD-1 or PD-L1 inhibitor (Powles *NEJM* 2021). EV has also demonstrated activity and a tolerable safety profile in cis-ineligible pts with la/mUC (Yu *Lancet Oncol* 2021). Given the efficacy of EV in la/mUC, it is being evaluated as perioperative therapy in cis-ineligible MIBC in EV-103 cohort L. **Methods:** Study EV-103 (NCT03288545) la/mUC and MIBC cohorts were described previously (Hoimes ASCO 2019; Hoimes ASCO-GU 2020). Cohort L was added to evaluate EV monotherapy (n = 50) as perioperative therapy in cis-ineligible pts with MIBC (cT2-T4aN0M0 or cT1-T4aN1M0). Eligible pts are previously untreated for MIBC, ECOG 0-2, have CrCl ≥30 mL/min, and are medically fit for and agree to undergo curative intent RC+PLND. Pts with pT1 disease are eligible only if they have N1 disease. Pts receive 3 cycles of neoadjuvant EV (1.25 mg/kg IV) on Days 1 and 8 of each 3-week cycle, followed by RC+PLND and then 6 cycles of adjuvant EV starting 8 weeks post-RC on the same schedule. Pathological complete response rate per central pathology review is the primary endpoint. Secondary endpoints include event-free survival and disease-free survival by blinded independent central review and investigator, pathological downstaging rate per central pathology review, OS, safety and tolerability. Cohort L is currently enrolling pts in the US and Canada. Clinical trial information: NCT03288545. Research Sponsor: Seagen Inc.

TPS588 **Trials in Progress Poster Session**

Sacituzumab govitecan (SG) plus enfortumab vedotin (EV) for metastatic urothelial carcinoma (UC) progressing on platinum-based chemotherapy and PD1/L1 inhibitors (ICB): Double antibody drug conjugate (DAD) phase I trial.

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Background: There have been multiple advances in therapy of advanced urothelial carcinoma following platinum and ICB; SG and EV are both FDA approved in this space though durations of response are short and overall survival limited at $<$ 13 months. Given different mechanisms of action, non-overlapping toxicities and potential for synergy, EV and SG is hypothesized to have manageable toxicities and demonstrate additive anti-tumor activity. **Methods:** NCT04724018 is a single-center (Dana-Farber/Harvard Cancer Center), open-label, non-randomized phase I trial using a Bayesian Optimal Interval design. SG and EV agents are administered intravenously (IV) on days 1 and 8 every 3 weeks (1 cycle) until progression or intolerable toxicities. Laboratory evaluation is performed on days 1 and 8 every cycle with additional blood collected throughout treatment for pharmacokinetic and antidrug antibody studies. Imaging is performed at baseline and every 6 weeks for the first 4 cycles followed by every 9 weeks thereafter. Up to 4 dose levels of the combination of SG and EV are studied with a starting dose of SG of 8 mg/kg and EV of 1 mg/kg (dose level 1) with additional dose escalations outlined in table. Dose de-escalation of SG to 6 mg/kg with the starting dose of EV 1 mg/kg (dose level -1) is permitted. A total of 3 to 18 patients are expected to be enrolled in current dose level depending on dose limiting toxicities (DLTs). DLT is assessed during cycle 1 of therapy and toxicities are captured up to 4 weeks after the last dose of therapy and being defined by $\geq$1 of the following: neutropenic fever, thrombocytopenic bleeding, grade 3 neuropathy, of any duration and any other grade $\geq$3 non-hematologic toxicity to include hyperglycemia (except alopecia) lasting $>$1 week or requiring $>$3 weeks interruption of therapy or dose reduction. The first patient per 3-patient cohort is required to complete 1 full cycle (3 weeks) before additional patients can be enrolled in that cohort. Therefore, up to 24 patients may be accrued. Trial continues to enroll at dose level one. Clinical trial information: NCT04724018. Research Sponsor: Gilead.

# of Patients	Dose Level	SG (D1, 8 q3wks)	EV (D1, 8 q3wks)
3-18	1 (starting doses)	8 mg/kg	1.0 mg/kg (maximum dose 100 mg)
3-18	2	8 mg/kg	1.25 mg/kg (maximum dose 125 mg)
3-18	3	10 mg/kg	1.25 mg/kg (maximum dose 125 mg)
3-18	- 1	6 mg/kg	1.0 mg/kg (maximum dose 100 mg/kg)

TPS589 **Trials in Progress Poster Session**

Study EV-302: A two-arm, open-label, randomized controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy in previously untreated advanced urothelial carcinoma (aUC) (trial in progress).

Michiel Simon Van Der Heijden, Shilpa Gupta, Matt D. Galsky, Christina Louise Derleth, Sue Lee, Ritesh S. Kataria, Thomas Powles; Netherlands Cancer Institute, Amsterdam, Netherlands; Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH; Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Seagen Inc., Bothell, WA; Astellas Pharma, Inc., Northbrook, IL; Merck & Co., Inc., Kenilworth, NJ; Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, London, United Kingdom

Background: Platinum-based chemotherapy is standard first line (1L) therapy for aUC. Maintenance therapy may be offered for patients (pts) who do not progress on 1L chemotherapy. However, not all pts are eligible for maintenance therapy, with many succumbing to their disease prior to 2L. Therefore, there is a persistent unmet need for safe and effective drug combinations in the 1L setting. Enfortumab vedotin (EV) is a Nectin-4 directed antibody-drug conjugate (ADC) comprised of a fully human mAb conjugated to the microtubule-disrupting agent, monomethyl auristatin E (MMAE), via a protease-cleavable linker. EV has previously shown an OS benefit vs chemotherapy in pts with locally advanced or metastatic urothelial carcinoma who had previously received platinum-based therapy and a PD-(L)1 inhibitor (Powles NEJM 2021). EV is FDA-approved in this and other settings (PADCEV, Seagen Inc., 2021). Preclinical studies showed that MMAE containing ADCs, including EV, induce evidence of immunogenic cell death and can enhance anti-tumor immunity, thereby laying the foundation for EV-PD-1/PD-L1 inhibitor combination (Liu Cancer Res 2020; Cao Can Res 2016). EV-302 will evaluate the efficacy and safety of EV+pembrolizumab (EV+P) combination vs gemcitabine+-cisplatin (gem+cis) or carboplatin (carbo) in pts with previously untreated aUC. **Methods:** EV-302/KN-A39 (NCT04223856) evaluates EV+P combination vs gem+cis or carbo in previously untreated pts with aUC. Eligibility criteria include pts with measurable disease, an ECOG status of $\leq$2, and eligible to receive EV, P, and cis or carbo. EV+P combination includes EV (1.25 mg/kg) administration on Days 1 and 8 with P (200 mg) on Day 1. Gem+cis or carbo includes: gem (1000 mg/m^2) on Days 1 and 8; and cis (70 mg/m^2) or carbo (AUC 4.5 or 5) on Day 1 of every 3-wk cycle. Randomization is 1:1 with stratification factors: cis eligibility, PD-L1 expression, and liver metastases. The primary endpoints are PFS and OS for EV+P compared to gem+cis or carbo. Other endpoints include ORR, duration of response, disease control rate, AEs, patient reported outcomes, PK, and biomarkers. The study opened March 2020 with sites actively enrolling globally. Clinical trial information: NCT04223856. Research Sponsor: Seagen Inc., Astellas Pharma, Inc., and Merck & Co., Inc.

TPS590 **Trials in Progress Poster Session**

An open-label, phase 2 study of personalized approach with perioperative immunotherapy for bladder preservation in muscle-invasive urothelial bladder carcinoma (MIBC).

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Background: Radical cystectomy (RC) without neoadjuvant chemotherapy is standard-of-care for cisplatin (cis)-ineligible pts (and those refusing cisplatin) with MIBC. Checkpoint inhibitors (CPIs) are being actively explored in the perioperative setting. CPIs documented a 42% pathologic complete response-rate (ypT0N0) in our previous trial (PURE-01, NCT02736266). In this trial, programmed cell-death ligand-1 (PD-L1) expression was associated with ypT0N0 response (*Necchi A, et al. Eur Urol. 2019)*, and a cohort of PD-L1+ pts who refused RC are still alive at long-term follow-up (*Bandini, Ann Oncol 2020*). Initial data from trials aimed at delivering a systemic therapy while sparing any local therapy on the bladder tumor in highly-selected pts are promising (*Galsky, 2021, Geynisman, 2021*). Sasanlimab (SASI) is a humanized, hinge region–stabilized (21) IgG4 mAb directed against human PD-1. Sasanlimab is currently being tested subcutaneously (SQ) in a phase III study in non-MIBC. Our hypothesis is that SASI can be offered in PD-L1+ pts as an exclusive therapeutic option instead of any additional treatment, after a clinical complete response (cCR) with an induction phase. **Methods:** This is a Phase 2, open-label, non-randomized, single-cohort study in pts with MIBC who are ineligible or unwilling to receive cisplatin-based neoadjuvant chemotherapy. The study will include pts with a PD-L1 CPS$\geq$10% in tumor biopsy.Other key inclusion criteria: UC histology, an ECOG PS 0$-$1. Cis-ineligibility is defined as one of the following: glomerular filtration rate $\geq$30 but $<$ 60 mL/min, or CTCAE v5 $\geq$grade 2 hearing loss or peripheral neuropathy. Key exclusion criteria: clinical evidence of $\geq$N1 or metastatic disease or UC in upper urinary tract; prior systemic therapy, radiation therapy, or prior RC. Pts will undergo a transurethral resection of the bladder (TURBT), a CT scan, and a ^{18}FDG-PET/CT scan. SASI will be administered SQ at the recommended dose of 300mg for a total of 3 cycles every 4 weeks prior to redo-TURBT. Pts who will achieve a cCR (i.e., no evidence of residual viable tumor at re-TURBT sample, urinary cytology and imaging tests) will receive additional SASI treatment for a total period of 12 months, every 4 weeks. Pts with non-CR will be excluded from the study and start treatment according to guidelines or investigator preference. Primary endpoint: event-free survival (EFS). Secondary endpoint: proportion of cCR. According to Simon's 2-stage MinMax design, a total of 55 pts will be included, and we anticipate the need for enrolling 110 pts for the neoadjuvant phase of the study. This assumption will correspond to the need for screening approximatively 220 pts onto this trial. Exploratory analyses will include: artificial intelligence through multiparametric bladder MRI/PET, and ctDNA analyses pre-post neoadjuvant period. Clinical trial information: 2021-001649-10. Research Sponsor: Ospedale San Raffaele, Pharmaceutical/Biotech Company.

TPS591 **Trials in Progress Poster Session**

Randomized phase II trial of gemcitabine, avelumab and carboplatin versus no neoadjuvant therapy preceding surgery for cisplatin-ineligible muscle-invasive urothelial carcinoma (MIUC): SWOG GAP trial (S2011).

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Background: Neoadjuvant cisplatin-based combination chemotherapy improves survival in cisplatin-eligible patients (pts) with muscle invasive bladder cancer (MIBC). An unmet need exists in cisplatin-ineligible pts with MIUC who are offered upfront surgery. Neoadjuvant immune checkpoint inhibitors (ICIs) have been demonstrated to be safe and active although the benefit may not extend to the majority of pts. The combination of GCa and an ICI has been demonstrated to be safe and active in cisplatin-ineligible metastatic urothelial carcinoma. In the neoadjuvant setting, combination GCa and an ICI may improve outcomes across a broad group of MIUC by delivering early systemic therapy to pts with cisplatin-ineligible MIUC. We hypothesized that the combination of GCa and avelumab, a PD-L1 inhibitor, may improve pathologic complete remissions (pCR) and long-term outcomes compared to upfront surgery for MIUC (S2011, NCT04871529). **Methods:** This multicenter, randomized (1:1), open-label phase II trial is comparing the combination of GCa and avelumab (Arm A) as neoadjuvant therapy vs. upfront surgery (Arm B) for pts with cisplatin-ineligible MIUC including MIBC and high-risk upper tract urothelial carcinoma (UTUC). Adjuvant therapy following radical cystectomy, nephroureterectomy or ureterectomy is deferred to investigator discretion in both arms. Eligible pts include those with MIBC or high-grade UTUC with a predominant urothelial component who are cisplatin-ineligible ($\geq$1 of: Zubrod performance status [PS] = 2, creatinine clearance [CrCl] 30 to $<$ 60 ml/min, neuropathy $>$ grade 1, hearing loss $>$ grade 1, congestive heart failure $>$ grade 2). The primary objective is pCR. The stratification factors include clinical stage (cT2N0M0 vs cT3-4aN0M0), Zubrod-PS (0-1 vs 2), CrCl (30 to $<$ 60 vs $\geq$ 60 ml/min). With 178 evaluable pts, the trial will have a power of 90% (using a 1-sided alpha 0.05) to detect pCR rate improvement from 15% to 35%. The secondary objectives are toxicities, resectability rates, surgical complications, event-free survival (EFS) and overall survival (OS). Correlative studies include tumor molecular profiling, blood immune studies, circulating tumor-DNA profiling and radiomics. Arm A receives gemcitabine 1000 mg/m^2 IV days 1, 8 every 3 weeks x 4 cycles, carboplatin AUC 4.5 (escalated to AUC 5 from cycle 2 if tolerated in cycle 1) IV day 1 every 3 weeks x 4 cycles and avelumab 800 mg IV day 1 every 2 weeks x 6 cycles. Surgery is performed 4-8 weeks after the last neoadjuvant administration. The trial is funded by NIH/NCI grants U10CA180888, U10CA180819, U10CA180821, U10CA180820, U10CA180868, and in part by EMD Serono, as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) and Pfizer. Clinical trial information: NCT04871529. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS592 **Trials in Progress Poster Session**

Attamage-A1: Phase I/II study of autologous CD8+ and CD4+ transgenic t cells expressing high affinity MAGE-A1-specific T-cell receptor (TCR) combined with anti-PD(L)1 in patients with metastatic MAGE-A1 expressing cancer.

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Background: Adoptive cellular therapies can lead to durable responses in treatment refractory leukemias and lymphomas; however, these approaches are still in early stage development for metastatic solid tumors. FH-MagIC TCR-T is an autologous CD8+ and CD4+ T cell product transduced with a transgenic T cell receptor (TCR) targeting MAGE-A1. MAGE-A proteins are classified within the "testis restricted" cancer testis antigens and are broadly expressed in a wide range of malignancies, including urothelial carcinomas, triple negative breast cancers (TNBCs) and non-small cell lung cancers (NSCLCs). Importantly, MAGE-A1 is undetectable in most normal tissues exclusive of the immune privileged testes, thereby making MAGE-A1 an ideal target for T cell immunotherapy approaches. Of note, FH-MagIC TCR-T is specific to the Class I HLA A*02:01-restricted MAGE-A1 epitope. Based on preclinical studies testing FH-MagIC-T in MAGE-A1 expressing tumor models, we have launched a Phase I/II study evaluating this autologous transgenic TCR therapy. **Methods:** This is a Phase I/II study testing FH-MagIC TCR-T cells in patients with metastatic urothelial carcinoma, TNBC or NSCLC. Eligible patients must have HLA type HLA-A*02:01 and demonstrate expression of MAGE-A1 on archival tumor tissue (≥1+ by immunohistochemistry). Patients must have been offered or received: i) anti-PD(L)1 therapy; ii) enfortumab vedotin (urothelial carcinoma patients); and iii) FDA-approved targeted therapies (e.g. NSCLC patients with actionable mutations in *EGFR*, *ROS1*, etc.). For each dose level (DL) in the Phase 1 portion, 1 patient will be treated without lymphodepletion (LD). If no dose limiting toxicities (DLT) are observed, the next 3 patients will receive LD with cyclophosphamide 300mg/m^2 and fludarabine 30mg/m^2 IV days -4 to -2 before T cell infusion. The first 4 patients will be treated at DL1: 1 x 10^9 cells. If no DLTs are observed, the next 4 patients will be treated at DL2: 5 x 10^9 cells. Otherwise, if a DLT is observed at DL1, the next 4 patients will be treated at DL-1: 5 x 10^8 cells. The Phase 2 portion of the trial will test FH-MagIC-TCR T cell product at the RP2D with the addition of standard of care anti-PD(L)1 therapy. Primary objectives are to assess safety (Phase 1) and radiographic response rate (Phase 2) per RECIST v1.1. Secondary objectives will evaluate progression free survival, overall survival, persistence of transgenic T cells in peripheral blood and migration into tumor tissue. For the Phase 2 portion, we assume a 5% null response rate (H0). If the true response rate with TCR-transduced cells is 25% (H1), 15 patients will yield 84% power at a one-sided alpha =.05. Clinical trial information: NCT04639245. Research Sponsor: SignalOne Bio.

TPS593 **Trials in Progress Poster Session**

SunRISe-1: Phase 2b study of TAR-200 plus cetrelimab, TAR-200 alone, or cetrelimab alone in participants with high-risk nonmuscle-invasive bladder cancer unresponsive to Bacillus Calmette-Guérin who are ineligible for or decline radical cystectomy.

Michiel Simon Van Der Heijden, Christopher Cutie, Shalaka Hampras, Charu Indoria, Rachel Stewart, Milin Acharya, Katherine Stromberg, Xiang Li, Neil Beeharry, John Maffeo, Joseph M Jacob; Netherlands Cancer Institute, Amsterdam, Netherlands; Janssen Research & Development, Clinical Oncology, Lexington, MA; Janssen Research & Development, Clinical Biostatistics, Raritan, NJ; Janssen Research & Development, Clinical Oncology, Spring House, PA; Janssen Reseach and Development, Clinical Biostatistics, Raritan, NJ; Upstate Medical University, Department of Urology, Syracuse, NY

Background: Treatment options are limited for patients with high-risk non-muscle-invasive bladder cancer (HR-NMIBC) unresponsive to intravesical bacillus Calmette–Guérin (BCG). TAR-200 is an intravesical drug delivery system for local continuous release of gemcitabine within the bladder. The current study will assess the rate of complete response (CR) upon treatment with TAR-200 + systemic cetrelimab (CET [anti–PD-1 antibody]), TAR-200, and CET in BCG-unresponsive participants with HR-NMIBC who are ineligible for or decline radical cystectomy (RC). **Methods:** SunRISe-1 (NCT04640623) is an open-label, parallel-group, multicenter phase 2b study designed to assess the efficacy and safety of TAR-200 + CET, TAR-200 alone, and CET alone in participants with BCG-unresponsive HR-NMIBC. Eligible participants are aged ≥ 18 years with ECOG PS 0, 1, or 2 and recurrent or persistent histologically confirmed HR-NMIBC (carcinoma in situ) with or without papillary disease (T1, high-grade Ta), who have been diagnosed within 12 months of last BCG treatment and are ineligible for or declined RC. Participants (N≈200) are randomized 2:1:1 to receive TAR-200 + CET (Cohort 1, n≈100), TAR-200 (Cohort 2, n≈50), or CET (Cohort 3, n≈50). In Cohorts 1 and 2, participants receive intravesical TAR-200 every 3 weeks through Week 24, and every 12 weeks thereafter until Week 96. In Cohorts 1 and 3, participants receive CET until Week 78. Primary disease assessments (cystoscopy, urine cytology, transurethral resection of bladder tumor [TURBT], and magnetic resonance imaging/computed tomography) are made at baseline; subsequent cystoscopy and centrally read urine cytology are performed every 12 weeks through Year 2, every 24 weeks until end of Year 3, and in Year 4 and Year 5 in accordance with institutional standards of care. TURBT is conducted at 24 and 48 weeks. The primary end point for the 3 cohorts is overall CR rate at any time point. Secondary end points include duration of response (ie, from time of first CR achieved to first evidence of recurrence, progression, or death [whichever is earlier] for participants who achieve a CR), overall survival, PK immunogenicity of cetrelimab, safety and tolerability, and patient-reported outcomes. Exploratory end points include incidence and time to cystectomy (measured from randomization to date of cystectomy), biomarkers, and health care resource utilization. This study opened in January 2021 and is enrolling participants at ≈165 study sites worldwide. Currently, the study is active in 13 countries with 12 participants enrolled as of September 12, 2021. Clinical trial information: NCT04640623. Research Sponsor: Janssen Research & Development, LLC.

TPS594 **Trials in Progress Poster Session**

EA8185: Phase 2 study of bladder-sparing chemoradiation (chemoRT) with durvalumab in clinical stage III, node positive urothelial carcinoma (INSPIRE), an ECOG-ACRIN/NRG collaboration.

Monika Joshi, Se Eun Kim, Abhishek A Solanki, David Tomoaki Miyamoto, David Degraff, Jennifer Wei Zou, Joshua J Meeks, Timur Mitin, Sean P. Collins, Edouard John Trabulsi, Noah M. Hahn, Jason A. Efstathiou, Michael Anthony Carducci; Penn State Cancer Institute, Hershey, PA; Dana Farber Cancer Institute-ECOG-ACRIN Biostatistics Center, Boston, MA; Loyola University Chicago, Maywood, IL; Massachusetts General Hospital and Harvard Medical School, Boston, MA; Pennsylvania State University College of Medicine, Hershey, PA; University of Pennsylvania, Philadelphia, PA; Jesse Brown VA Medical Center, Chicago, IL; Department of Radiation Medicine, Oregon Health and Science University, Portland, OR; Department of Radiation Medicine, Georgetown University, Washington, DC; Department of Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; Johns Hopkins Greenberg Bladder Center Institute, Johns Hopkins School of Medicine, Baltimore, MD; Johns Hopkins Kimmel Cancer Ctr, Baltimore, MD

Background: Patients [pts] withlymph node positive (LN+), non-metastatic bladder cancer (BC) have a better prognosis than those with metastatic (M1) disease. However, this population is under-represented in advanced bladder trials and ineligible for bladder-sparing trials. Therefore, there have been no larger prospective trials establishing the standard of care in LN+ BC. Given the promise of immunotherapy in advanced BC and potential synergy between immunotherapy and radiation, INSPIRE was designed to determine the role of concurrent and adjuvant durvalumab (durva) in this patient population when treated with induction chemotherapy (IC) followed by concurrent chemoRT. **Methods:** This is a randomized phase II study that is enrolling BC pts with stage III [N1-3 M0], pure or mixed urothelial cancer. Pts must have received ≥3 cycles of IC [either before or after registration, prior to randomization] without progression. LN+ is defined as radiologically LN ≥1.0 cm in short axis, with or without biopsy prior to IC. As long as pts do not progress on induction chemotherapy, they will be randomized to chemoRT+/- durva using 5 stratification factors (Simon Pocock minimization method) a) IC prior vs. post registration b) cisplatin vs non-cisplatin regimen during RT c) LN size d) response to IC e) extent of TURBT. Pts on the chemoRT+durva arm will get chemotherapy per physician choice + IMRT + 3 x doses of Q3wk durva for 6.5-8 wks, whereas those on the control arm will get chemoRT alone. The primary end point is clinical complete response [CR], defined as no radiologically measurable disease in the LNs and negative cystoscopy and bladder biopsy 8-10 weeks post-chemoRT +/- durva. Pts on the chemoRT + durva arm who have a CR or clinical benefit (>T0 and ≤T2 in bladder per cystoscopy, biopsy + CR/PR/SD in LN by imaging) will get adjuvant Q4wk durva for 9 doses, while those on the chemoRT arm will undergo observation. Secondary end points include OS, PFS, bladder-intact event-free survival, rate of toxicity and salvage cystectomy. This study is designed to detect an absolute improvement of 25% in clinical CR between both arms (37.5% to 62.5%). The accrual goal is 114, assuming 10% drop out + anticipating that 20% chemotherapy-naïve pts will progress post IC, and 92 evaluable pts that will provide 81% power to detect this difference using a Fisher's exact test. We are banking blood and primary tumor tissue pre- and post-chemoRT in both groups. The study was activated in August 2020 and accrual is ongoing. We expanded eligibility to include N3 in 9/2021. INSPIRE is the first prospective study designed for only LN+ BC and will define both short-term and long-term outcomes for bladder sparing in this patient population and has the potential to define a new treatment strategy for stage III BC. Clinical trial information: NCT04216290. Research Sponsor: U.S. National Institutes of Health.

TPS595 **Trials in Progress Poster Session**

Phase Ib trial of erdafitinib (E) combined with enfortumab vedotin (EV) following platinum and PD-1/L1 inhibitors for metastatic urothelial carcinoma (mUC) with FGFR2/3 genetic alterations (GAs).

Rohit K. Jain, Youngchul Kim, Jennifer Rembisz, Richard Piekarz, Timothy W. Synold, Jingsong Zhang, Guru P. Sonpavde; H. Lee Moffitt Cancer Center, Tampa, FL; Department of Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; City of Hope, Duarte, CA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Erdafitinib and enfortumab vedotin are available treatment options in mUC patients with somatic FGFR2/3 GAs after progression on platinum-based chemotherapy and PD-1/L1 inhibitors. However, due to decline in their clinical condition, the sequential delivery of these agents is challenging. Tubulin antagonists induce a G2-M cell-cycle block, while FGFR inhibitors cause a G1 block, with studies suggesting that their combination may be additive or synergistic. Retrospective studies suggest that the activity of EV is not compromised by somatic FGFR2/3 GAs. Hence, there is rationale to evaluate the feasibility of the combination of EV and E, to overcome the difficulties of resistance and sequencing these agents in mUC patients with FGFR2/3 GAs. **Methods:** This is a phase Ib, single arm, multicenter study in patients with mUC harboring somatic FGFR2/3 GAs who have progressed after platinum and PD-1/L1 inhibitor therapies with enrollment of up to 30 patients. Pts are required to have predominant urothelial component, ECOG-PS 0-2, neuropathy ≤ grade 1 and no ophthalmologic conditions precluding treatment with E. FGFR2/3 GAs may be identified by tumor tissue or circulating tumor (ct)-DNA profiling. The primary objective is feasibility and establishing a recommended phase-2 dose (RP2D). Secondary objectives include objective response rate, duration of response, progression-free survival and overall survival. The dose-escalation component will enroll up to 18 pts with 3+3 design (dosing cohorts in table), followed by dose-expansion component of 12 pts. The dose limiting toxicities (DLTs) will be evaluated using a sequential Bayesian toxicity monitoring that allows a maximum DLT rate of 0.33 during the dose-expansion phase. Exploratory biomarker analyses will be performed including 1) tumor PD-L1, Nectin-4 assessment by immunohistochemistry and association with response 2) ct-DNA evaluation at baseline and progression to evaluate resistance pathways 3) pharmacokinetic studies will assess plasma levels of E and free monomethyl auristatin-E (MMAE). This is led by North American Star Consortium as part of Experimental Therapeutics. Clinical trial information: NCT04963153. Research Sponsor: U.S. National Institutes of Health.

	Dose		
Dose Level	E	EV	Cycle Length
-1	8 mg PO QD	0.75 mg/kg IV (maximum dose 75 mg) D1,8,15	28 days
1	8 mg PO QD	1 mg/kg IV (maximum dose 100 mg) D1,8,15	
2	8 mg PO QD	1.25 mg/kg IV (maximum dose 125 mg) D1,8,15	

TPS596 **Trials in Progress Poster Session**

PIVOT IO 009: A phase 3, randomized study of neoadjuvant and adjuvant nivolumab (NIVO) plus bempegaldesleukin (BEMPEG; NKTR-214) versus NIVO alone versus standard of care (SOC) in patients (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin (cis)-ineligible.

Petros Grivas, Michiel Simon Van Der Heijden, Andrea Necchi, Arlene O. Siefker-Radtke, Hernan Cutuli, Anila H. Qureshi, Stephanie Kreiser, Moana Hodari, Shruthi Ravimohan, Yousef Zakharia; University of Washington, Seattle, WA; Netherlands Cancer Institute, Amsterdam, Netherlands; Vita-Salute San Raffaele University and IRCCS San Raffaele Hospital, Milan, Italy; MD Anderson, Houston, TX; Hospital Sirio Libanes, Buenos Aires, Argentina; Bristol Myers Squibb, Princeton, NJ; University of Iowa, Iowa City, IA

Background: Radical cystectomy (RC) without neoadjuvant chemotherapy remains SOC for cis-ineligible pts (and those refusing cis) with MIBC and T1-T4aN1 disease. Yet, many pts progress to incurable, metastatic disease. Preventing disease recurrence for these pts remains an unmet need. Immune checkpoint inhibitors (ICIs) are approved in Bacillus Calmette-Guérin-unresponsive carcinoma in situ, in the adjuvant and metastatic urothelial cancer (UC) settings, and are being actively explored in the perioperative setting. In phase 2 single-arm trials, neoadjuvant ICIs showed promising pathologic complete response (pCR) rates (approximately 30%–40%). The phase 3 CheckMate 274 study showed improved disease-free survival with adjuvant NIVO vs placebo in MIBC. BEMPEG, an immunostimulatory interleukin-2 (IL-2) cytokine prodrug, is engineered to deliver a controlled, sustained, and preferential signal to the clinically validated IL-2 pathway. Preferential binding of BEMPEG to the IL-2 heterodimeric receptor (IL-2R$\beta\gamma$) activates and expands CD8+ T cells and natural killer cells over immunosuppressive regulatory T cells. The combination of BEMPEG + NIVO demonstrated deep responses and a tolerable safety profile in pts with metastatic UC in the phase 1/2 PIVOT-02 trial and is being further explored in the phase 2 PIVOT-10 (NCT03785925) study. The PIVOT IO 009 study, presented here, aims to evaluate the hypothesis that perioperative treatment with BEMPEG + NIVO will provide higher pCR and longer event-free survival (EFS) vs SOC in cis-ineligible pts with MIBC and T1-T4aN1 disease. **Methods:** PIVOT IO 009 (NCT04209114) is an open-label, phase 3 trial of 540 cis-ineligible pts with MIBC and T1-4aN1 disease, who will be randomized 1:1:1 to receive SOC, neoadjuvant and adjuvant BEMPEG + NIVO, or neoadjuvant and adjuvant NIVO alone. Stratification factors include clinical stage (T2N0 vs T3-T4aN0 vs T1-T4aN1) and tumor cell PD-L1 status. Key inclusion criteria: adults with MIBC and T1-T4aN1 disease deemed eligible for RC and ECOG PS 0–1. Cis-ineligibility is defined as one of the following: glomerular filtration rate ≥30 but $<$ 60 mL/min, or ≥grade 2 hearing loss or peripheral neuropathy. Key exclusion criteria: clinical evidence of ≥N2 or metastatic disease or UC in the upper urinary tract; prior systemic therapy, radiation therapy, or prior surgery for bladder cancer other than TURBT or biopsies. Primary endpoints: pCR rate (pT0N0) of neoadjuvant BEMPEG + NIVO vs no neoadjuvant therapy (SOC), and EFS of neoadjuvant and adjuvant BEMPEG + NIVO vs SOC. Secondary endpoints: pCR rate of neoadjuvant NIVO vs SOC; EFS of neoadjuvant and adjuvant NIVO vs SOC; overall survival and safety in each treatment arm vs SOC. The study is currently recruiting pts. Clinical trial information: NCT04209114. Research Sponsor: Bristol Myers Squibb.

TPS597 **Trials in Progress Poster Session**

Randomized comparator-controlled study evaluating efficacy and safety of pembrolizumab plus Bacillus Calmette-Guérin (BCG) in patients with high-risk nonmuscle-invasive bladder cancer (HR NMIBC): KEYNOTE-676 cohort B.

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Background: Cohort A of the phase 2 KEYNOTE-057 study showed that pembrolizumab monotherapy provided effective antitumor activity and acceptable safety in patients with BCG-unresponsive HR NMIBC with carcinoma in situ (CIS). Pembrolizumab in combination with BCG at earlier stages of HR NMIBC might provide benefit superior to that of BCG monotherapy. The open-label, comparator-controlled, phase 3 KEYNOTE-676 study (NCT03711032) will be conducted to investigate the efficacy and safety of pembrolizumab + BCG versus BCG monotherapy in patients with HR NMIBC. Cohort A will enroll patients with persistent or recurrent HR NMIBC after BCG induction. Cohort B is a new, randomly assigned cohort that will help evaluate pembrolizumab + BCG in BCG treatment–naive patients who either never received BCG treatment or received BCG treatment $>$ 2 years before enrollment. **Methods:** Cohort B of KEYNOTE-676 will enroll approximately 975 patients with blinded independent central review (BICR)–confirmed HR NMIBC (T1, high-grade Ta CIS) and Eastern Cooperative Oncology Group performance status score 0-2 who underwent cystoscopy/transurethral resection of bladder tumor $\leq$12 weeks before randomization and had not received BCG within the past 2 years. Patients will be randomly assigned 1:1:1 to receive pembrolizumab 400 mg intravenously (IV) every 6 weeks (Q6W) + BCG reduced maintenance ($\leq$6 months), pembrolizumab 400 mg IV Q6W + BCG full maintenance ($\leq$18 months), or BCG monotherapy (BCG full maintenance). Stratification factors include NMIBC stage (CIS or no CIS) and PD-L1 expression (combined positive score [CPS] $\geq$10 or CPS $<$ 10), determined by central laboratory. Disease status will be assessed by use of cystoscopy, urine cytology, and biopsy (as applicable) every 12 weeks (Q12W) through year 2, then every 24 weeks through year 5; imaging with computed tomography urography will occur every 72 weeks. Adverse events (AEs) will be monitored throughout the study and up to 30 days after cessation of study treatment (90 days for serious AEs). The primary end point is event-free survival (EFS). Secondary end points include complete response rate by BICR, duration of response (DOR), 12-month DOR rate (CIS only), 24-month EFS rate, disease-specific survival, time to cystectomy, overall survival, and safety. The study is enrolling or planning to enroll at sites in Asia, Australia, Europe, North America, and South America. Clinical trial information: NCT03711032. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS598 **Trials in Progress Poster Session**

A phase 3, single-arm study of CG0070 in subjects with nonmuscle invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guerin (BCG).

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Background: CG0070 is a serotype 5 adenovirus engineered to express GM-CSF and replicate in cells with mutated or deficient RB, with response rates (RR) of approximately 45% observed in patients with recurrent NMIBC after BCG (J Urol. 2012;188:2391–7; Urol Oncol. 2018;36(10):440–7). This single arm phase 3 study (NCT04452591) was launched to confirm the clinical activity of CG0070 in patients with BCG Unresponsive NMIBC. **Methods:** 110 patients with BCG-unresponsive CIS with or without concurrent Ta or T1 disease will be treated with intravesical (IVe) CG0070 at a dose of $1x10^{12}$ vp. CG0070 will be administered as follows: induction weekly x 6 followed by weekly x 3 maintenance instillations at months 3, 6, 9, 12, and 18. Patients with persistent CIS or HG Ta at 3 months (m) may receive re-induction with weekly x 6 CG0070. Assessment of response will include q 3 m cystoscopy with biopsy of areas suspicious for disease, urine cytology, CTU/MRU, and mandatory bladder mapping at 12 m. Detection of high grade disease within the bladder will be enumerated as recurrence or non-response. The primary endpoint of the study is CR at any time on study as assessed by biopsy (directed to cystoscopic abnormalities and mandatory mapping at 12 m), urine cytology, and radiography, as above. Secondary endpoints include CR at 12 m, duration of response, progression free survival, cystectomy free survival and safety. Correlative assessments include changes in the tumor immune microenvironment, systemic immune induction as reflected in the peripheral blood and urine, as well as viral replication and transgene expression. Baseline expression of coxsackie adenovirus receptor, E2F transcription factor as well as anti-adenovirus antibody titer will be correlated with tumor response. Study enrollment globally is ongoing including in North America, Taiwan, Japan, and South Korea. Refs. Burke JM, Lamm DL, Meng MV, Nemunaitis JJ, Stephenson JJ, Arseneau JC, Aimi J, Lerner S, Yeung AW, Kazarian T, Maslyar DJ, McKiernan JM. A first in human phase 1 study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. Clinical trial information: NCT04452591. Research Sponsor: CG Oncology.

TPS599 **Trials in Progress Poster Session**

Randomized phase 2 umbrella study of various neoadjuvant therapies for patients with muscle-invasive urothelial carcinoma of the bladder (MIBC) who are cisplatin-ineligible or refuse cisplatin therapy and undergoing radical cystectomy (Optimus).

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Background: A growing body of data support that the key to generating anti-tumor immune responses triggered by administration of immuno-oncology (IO) agents, is the activation and invasion of T lymphocytes. Checkpoint inhibitors (CPIs) are being actively explored in the neoadjuvant setting of MIBC. CPIs documented 30-40% pathologic complete response-rates (ypT0N0) in previous trials. Increasingly, novel IO agents are being developed in combinations with anti PD(L)-1 therapies. Understanding the changes in the tumor microenvironment that occur with the addition of novel immunomodulating agents to PD(L)-1 inhibitors can help inform whether a compound is viable for further development. The OPTIMUS trial is a window of opportunity, neoadjuvant platform design study in MIBC patients that are cisplatin-ineligible. The study investigates the addition of the indoleamine 2, 3-dioxygenase 1 (IDO1) inhibitor epacadostat to the PD-1 inhibitor retifanlimab. The platform design allows for investigation of other novel immune-modulating combinations. **Methods:** This is an open-label, randomized, Phase 2, multi-treatment group, window-of-opportunity, platform study for participants with MIBC undergoing radical cystectomy who refuse or are not eligible for cisplatin-based neoadjuvant chemotherapy (NCT04586244). Participants are randomized based on tumor tissue PD-L1 CPS $\geq$ 10 or PD-L1 CPS $<$ 10 to one of the following treatment groups: Treatment Group A (epacadostat + retifanlimab); Treatment Group B (retifanlimab monotherapy); Treatment Group C (epacadostat monotherapy). 18 patients will be enrolled in each of Treatment Groups A and B. 9 patients will be enrolled into Treatment Group C. Total treatment duration is a maximum of 10 weeks. The platform study design allows for addition of future treatment groups. Pre-treatment biopsy is obtained through transurethral resection of bladder tumor (TURBT), followed by neoadjuvant treatment, followed by radical cystectomy. In all treatment groups, tissue from the surgical specimen(s) is collected and compared with the initial pre-treatment samples. The primary endpoint is the change from baseline in CD8+ lymphocytes within resected tumor. Secondary endpoints include safety and tolerability, rates of ypT0N0 response, and major pathologic response. Exploratory analyses include tumoral changes in gene cell expression profile, immune-cell protein and metabolic marker levels, and spatial relationships between cell types. Plasma is also collected and will be investigated for changes in cytokines and other inflammatory or metabolic markers. Clinical trial information: NCT04586244. Research Sponsor: Incyte Corporation.

TPS600 **Trials in Progress Poster Session**

A prospective, single-center, phase II randomized controlled trial to evaluate the safety, feasibility, and preliminary efficacy of exercise during intravesical therapy for nonmuscle invasive bladder cancer.

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Background: Non-muscle invasive bladder cancer (NMIBC) accounts for about 75% of newly diagnosed bladder cancers. The treatment for NMIBC initially involves transurethral resection of the bladder tumor followed by six weeks of induction intravesical therapy. NMIBC has a high rate of recurrence (31-78%) and progression (15%). Moreover, bladder cancer and its treatments may affect patient functioning, quality of life, and increase the risk of cardiovascular mortality. Exercise is a safe and effective intervention for many cancer patients groups, however, no studies have examined exercise during intravesical therapy for NMIBC. Bladder cancer and exeRcise trAining during intraVesical thErapy (BRAVE) is the first phase II randomized controlled trial designed to evaluate the safety, feasibility, and preliminary efficacy of exercise for NMIBC patients during intravesical therapy. An exploratory aim is to track the short-term bladder cancer recurrence and progression rates for each trial arm. **Methods:** BRAVE has a target sample size of 66 men or women diagnosed with NMIBC undergoing intravesical therapy with chemotherapy or immunotherapy agents. Participants are being randomly assigned to usual care or exercise intervention, which consists of three supervised, high-intensity interval training sessions/week for 12-weeks. Safety is being evaluated by any adverse events during the physical fitness assessments or exercise sessions. Feasibility will be evaluated by eligibility, recruitment, adherence, and attrition rates. Preliminary efficacy endpoints are cardiorespiratory fitness assessed by peak oxygen consumption (VO_{2peak}) at 6-week (post-intravesical therapy) and 3-month surveillance cystoscopy; and complete response (CR), defined as negative cytology, imaging, and cystoscopy and, when indicated, a negative biopsy. CR will be assessed at 3-month and one-year surveillance cystoscopy follow-up. Statistical analyses will follow the intention-to-treat approach. Analysis of covariance will compare between-group VO_{2peak} differences at post-intervention (pre-cystoscopy). Study enrolment started May 24, 2021 and is ongoing. As of October 4, 2021, we have screened 17 NMIBC patients scheduled for intravesical therapy for eligibility; 16 (94%) were ineligible for medical (n = 11), language (n = 3), or location (n = 2) reasons. All the medical reasons included severe cardiovascular diseases. One eligible patient declined due to travel distance to the facility. In the face of a slower-than-expected recruitment rate, eligibility was extended to patients in the maintenance phases of treatment for NMIBC, where patients receive three weekly instillations of intravesical therapy. Clinical trial information: NCT04593862. Research Sponsor: Alberta Cancer Foundation/Alberta Cancer Clinical Trials - Provincial Investigator-Initiated Trial Competition.