First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab vs placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma (MIUC).

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Background: The standard of care (SOC) for patients (pts) with MIUC is radical surgery ± cisplatin-based neoadjuvant chemotherapy (chemo), but many pts are cisplatin-ineligible. There is no conclusive evidence supporting adjuvant chemo in pts who did not receive neoadjuvant chemo and in those with residual disease after neoadjuvant cisplatin. This phase 3 trial of adjuvant nivolumab (NIVO) vs placebo (PBO) in pts with MIUC after radical surgery ± neoadjuvant cisplatin (CheckMate 274) aims to address an unmet need in these pts. We report the initial results. **Methods:** This is a phase 3, randomized, double-blind, multicenter trial of NIVO vs PBO in pts with high-risk MIUC (bladder, ureter, or renal pelvis) after radical surgery. Pts were randomized 1:1 to NIVO 240 mg Q2W or PBO for ≤ 1 year of adjuvant treatment. Pts had radical surgery within 120 days ± neoadjuvant cisplatin or were ineligible/declined cisplatin-based chemo, evidence of UC at high risk of recurrence per pathologic staging, were disease-free by imaging, and ECOG PS ≤ 1. Primary endpoints: disease-free survival (DFS) in all randomized pts (ITT population) and in pts with tumor PD-L1 expression ≥ 1%. DFS was stratified by nodal status, prior neoadjuvant cisplatin, and PD-L1 status. Non–urothelial tract recurrence-free survival (NUTRFS) in ITT pts and in pts with PD-L ≥ 1% is a secondary endpoint. Safety is an exploratory endpoint. **Results:** In total, 353 pts were randomized to NIVO (PD-L1 ≥ 1%, n = 140) and 356 pts to PBO (PD-L1 ≥ 1%, n = 142). The primary endpoint of DFS was met in ITT pts (median follow-up, 20.9 mo for NIVO; 19.5 mo for PBO) and in pts with PD-L1 ≥ 1%. DFS and NUTRFS were improved with NIVO vs PBO in both populations (Table). DFS improvement with NIVO was generally consistent across subgroups. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 17.9% and 7.2% of pts in the NIVO and PBO arms, respectively. **Conclusions:** NIVO demonstrated a statistically significant and clinically meaningful improvement in DFS vs PBO for MIUC after radical surgery, both in ITT pts and pts with PD-L1 ≥ 1%. AEs were manageable and consistent with previous reports. These results support adjuvant NIVO as a new SOC for pts with MIUC with high risk for recurrence despite neoadjuvant chemo or those ineligible for and/or declining cisplatin-based chemo. Clinical trial information: NCT02632409. Research Sponsor: Bristol Myers Squibb.

		NIVO	PBO	HR (CI)
Median DFS (95% CI), mo	**ITT**	21.0 (17.1–33.4)	10.9 (8.3–13.9)	0.70 (0.54–0.89)[a]; *P* = 0.0006
	PD-L1 ≥ 1%	NR (22.0–NE)	10.8 (5.7–21.2)	0.53 (0.34–0.84)[b]; *P* = 0.0004
Median NUTRFS (95% CI), mo	**ITT**	24.6 (19.2–35.0)	13.7 (8.4–20.7)	0.72 (0.58–0.89)[c]
	PD-L1 ≥ 1%	NR (26.0–NE)	10.9 (5.8–22.1)	0.54 (0.38–0.77)[c]
Any-grade TRAEs, n (%)		272 (77.5)	193 (55.5)	–
Grade 3–4 TRAEs, n (%)[d]		63 (17.9)	25 (7.2)	

[a]98.31% CI. [b]98.87% CI. [c]95% CI. [d]There were 2 deaths due to pneumonitis in the NIVO arm. NE, not estimable; NR, not reached.

Socio-environmental conditions associated with geospatial clusters of urothelial carcinoma: A multi-institutional analysis.

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Background: Industrial byproducts and environmental pollutants (IBP/EP) are associated with the development of urothelial carcinoma (UC). While tobacco exposure (TE) is the major risk factor for UC, the interaction between sources of IBP/EP and incidence of UC in surrounding communities has been infrequently explored. We seek to identify high-density microregions of UC prevalence and spatially-related industrial and environmental risk factors. **Methods:** We queried a multi-institutional database for patients diagnosed with UC between 2008-2018. Geocoded addresses and ArcGIS software were used to calculate the Getis-Ord-Gi* statistic and perform hotspot analysis on the census-block level to identify UC hotspots. Demographics, clinicopathologic disease characteristics, and proximity to sources of IBP/EP were compared using Pearson's chi-square and Student's T-test. Univariate analyses and multivariable multilevel logistic random-intercept regression models were fitted to test the association between patient and census block-level factors and living in a UC hot spot. **Results:** Of 5,080 patients meeting inclusion/exclusion criteria, 148 patients (2.9%) were associated with one of three UC hotspots. In univariate analyses, hotspot patients were less likely to be tobacco users (OR 0.24, p=0.004) or of white race (OR 0.10, p<0.001) and less likely to have higher income (OR 0.73, p=0.005). They were more likely to be associated with IBP/EP exposure (OR 8.24, p=0.001) (Table). Multivariable analysis confirmed increased likelihood of residing in a UC hotspot and proximity to high-traffic density (OR >999, p=<0.001) and sites of IBP/EP contamination (OR 106.90, p=0.009), with decreased likelihood of tobacco use (OR 0.11, p=0.045) and white race (OR 0.02, p=0.004). **Conclusions:** Patients residing in geospatial hotspots of UC prevalence are less likely to be white, higher income or tobacco users and more likely to reside in proximity to sources of IBP/EP. Further research is necessary to investigate the interplay between socioeconomic status, race and environmental risk factors in order to better identify at-risk populations and improve screening, referral, diagnosis and timely intervention. Research Sponsor: Sharpe-Strumia Research Foundation.

Univariate multilevel logistic regression models (random intercept models).

	OR	LCL	UCL	*p*
Age at Diagnosis (Years)	0.97	0.94	1.02	0.226
Male	0.44	0.16	1.22	0.115
White (Ref=Black, Asian, Hispanic, Other)	**0.10**	**0.05**	**0.19**	**<0.001**
Tobacco	**0.24**	**0.09**	**0.63**	**0.004**
Industrial/Occupational Exposure	3.51	0.22	56.30	0.376
Any Exposure	**8.24**	**2.37**	**28.70**	**0.001**
Live within 1,000 Yards of Traffic Hotspot	**>999**	**>999**	**>999**	**<0.001**
Live within 1,000 Yards of an Industrial Site	**8.78**	**2.44**	**31.66**	**0.001**
Median Yearly Household Income (in $10,000 Increments)	**0.73**	**0.58**	**0.91**	**0.005**

393 **Oral Abstract Session**

Primary results of EV-301: A phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated locally advanced or metastatic urothelial carcinoma.

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Background: Patients with locally advanced or metastatic urothelial carcinoma (la/mUC) have poor survival following progression after platinum-containing chemotherapy and PD-1/L1 inhibitor regimens. Enfortumab vedotin (EV) is an antibody-drug conjugate directed to Nectin-4, a cell adhesion molecule highly expressed in urothelial carcinoma, with remarkable efficacy observed in a single-arm trial in this setting. This randomized phase III study (EV-301) was performed to confirm these findings. **Methods:** EV-301 (NCT03474107) is a global, open-label phase III study of EV vs chemotherapy conducted in patients with la/mUC who had received a prior platinum-containing chemotherapy and had disease progression during or after PD-1/L1 inhibitor treatment. Patients were randomized 1:1 to receive EV (1.25 mg/kg) on Days 1, 8, and 15 of each 28-day cycle or investigator choice of standard docetaxel, paclitaxel, or vinflunine chemotherapy. The primary endpoint was overall survival (OS); secondary endpoints included investigator-assessed progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) per RECIST v1.1, as well as safety/tolerability. A prespecified interim analysis, which tested OS at an adjusted 1-sided significance level of $P = 0.00679$, was performed when ≥285 deaths had occurred. The results of this interim analysis are presented here. **Results:** Overall, 608 patients with la/mUC were randomly assigned to EV (n=301) or chemotherapy (n=307). As of July 15, 2020, 301 deaths had occurred (EV, n=134; chemotherapy, n=167). After an 11.1 mo follow-up, median OS was significantly prolonged by 3.9 mo with EV compared with chemotherapy (median OS: 12.9 vs 9.0 mo, respectively; HR=0.70 [95% CI: 0.56-0.89], 1-sided P =0.001). Additionally, the OS benefit of EV was retained in the majority of prespecified subgroups. Progression-free survival also was improved with EV (5.6 mo) vs chemotherapy (3.7 mo) (HR=0.61 [95% CI: 0.50-0.75]; 1-sided P <0.00001). Both ORR and DCR were significantly higher with EV vs chemotherapy (40.6% vs 17.9% and 71.9% vs 53.4%, respectively; 1-sided P <0.001 each). Rates of treatment-related adverse events (TRAEs; 93.9% vs 91.8%), including serious TRAEs (22.6% vs 23.4%), were comparable between the EV and chemotherapy groups. Rates of grade ≥3 TRAEs were ~50% in both groups; decreased neutrophil count (13.4%) and white blood cell count (6.9%) were more common in the chemotherapy group, and maculo-papular rash (7.4%) was more common in the EV group. **Conclusions:** EV is the first therapy to show significant survival advantage over standard chemotherapy in patients with treatment-experienced la/mUC. With robust clinical benefit and a tolerable safety profile, EV is a new standard of care for this aggressive disease. Clinical trial information: NCT03474107. Research Sponsor: Astellas Pharma, Inc., Pharmaceutical/Biotech Company.

EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors.

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Background: Cisplatin (cis)-ineligible, platinum-naive patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) who progress on/after PD-1/L1 inhibitors (PD-1/L1-i) have a poor prognosis and few treatment (tx) options. Enfortumab vedotin (EV) is an antibody-drug conjugate directed against Nectin-4, an immunoglobulin-like cell adhesion molecule highly expressed in UC. EV-201 (NCT03219333) is a pivotal, single-arm, 2-cohort study of EV in la/mUC; Cohort (C) 1 data led to FDA accelerated approval of EV in adult pts with la/mUC who previously received a PD-1/L1-i and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, la/mUC setting. Here, we present the primary analysis from C2: cis-ineligible pts with prior PD-1/L1-i and no prior platinum for la/mUC. **Methods:** Pts in this open-label, multicenter, multinational study received 1.25 mg/kg EV on Days 1, 8, and 15 of each 28-day cycle. Primary endpoint was confirmed objective response rate (ORR) per RECIST 1.1 by blinded independent central review (BICR). Secondary endpoints were duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** As of 08 Sep 2020 (data cutoff), 91 pts were enrolled and 89 treated in C2. Pts were elderly (median age: 75 y [range: 49-90]) with comorbidities, including moderate/severe renal impairment. Pts were cis-ineligible at study entry due to CrCl $<$ 60 mL/min (66%), Grade $\geq$2 hearing loss (15%), or ECOG PS 2 (7%); an additional 12% met $\geq$1 criterion. The primary tumor site was in upper tract in 43%; 79% had visceral mets, including 24% with liver mets. Median (m) tx duration was 6.0 mo (range: 0.3 – 24.6). Confirmed ORR per BICR was 52% (95% CI: 40.8–62.4), including 20% CR among treated pts. mDOR was 10.9 mo (95% CI: 5.8–NR). mPFS and mOS were 5.8 mo (95% CI 5.0-8.3) and 14.7 mo (95% CI 10.5-18.2), respectively. Most common all-grade tx-related AEs were alopecia (51%), peripheral sensory neuropathy (47%), and fatigue (34%). Tx-related AEs of interest included rash (61% all grade, 17% $\geq$G3), peripheral neuropathy (54% all grade, 8% $\geq$G3), and hyperglycemia (10% all grade, 6% $\geq$G3). Four deaths were reported as tx related by investigators, all in pts $\geq$75 y with multiple comorbidities: 3 events $\leq$30 d of first EV dose in pts with BMI $\geq$30(acute kidney injury, metabolic acidosis, and multiple organ dysfunction syndrome) and 1 event $>$ 30 d after last dose (pneumonitis). **Conclusions:** In EV-201 C2, the majority of platinum-naive, cis-ineligible la/mUC pts who progressed on/after PD-1/L1-i achieved durable responses to EV, with 1/5 achieving CR. PFS and OS were encouraging. Safety was consistent with the previously reported AE profile of EV, within the context of a patient population with advanced malignancy and comorbidity. These data show the potential for EV as a non-platinum option following PD-1/L1-i. Clinical trial information: NCT03219333. Research Sponsor: Seagen Inc.

395 **Rapid Abstract Session**

Cost-effectiveness analysis of pembrolizumab for BCG-unresponsive carcinoma in situ of the bladder.

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Background: Patients with BCG-unresponsive carcinoma in situ (CIS) are treated with radical cystectomy (RCx) or salvage intravesical chemotherapy (SIC). Recently, the FDA approved pembrolizumab for BCG-unresponsive CIS +/- papillary tumors. Given the costs and toxicities of pembrolizumab, it remains unclear whether its benefits are sufficient to warrant widespread use for BCG-unresponsive CIS. To that end, we conducted a cost-effectiveness analysis comparing pembrolizumab with RCx and SIC (using gemcitabine-docetaxel as the prototypical regimen) for patients with BCG-unresponsive CIS. **Methods:** A decision-analytic Markov model compared pembrolizumab, SIC (with gemcitabine-docetaxel), and RCx for patients with BCG-unresponsive CIS +/- papillary tumors who are RCx candidates (index patient 1) or are unwilling/unable to undergo RCx (index patient 2). Each treatment option was a Markov node containing distinct variations of the following health states: surveillance, recurrence, progression to MIBC, progression to metastasis, treatment toxicity, and death. Incremental Cost-Effectiveness Ratios (ICERs) were compared using a willingness-to-pay threshold of $100,000/Quality-adjusted life year (QALY). The model used a US Medicare perspective with a 5-year time horizon for the base case. One-way and probabilistic sensitivity analyses were performed for all model parameters. **Results:** For index patient 1, pembrolizumab was not cost-effective vs. RCx (ICER $1,403,008) or SIC (ICER $2,011,923). One-way sensitivity analysis revealed that pembrolizumab only became cost-effective relative to RCx with a $>$ 93% price reduction. Relative to RCx, SIC was cost-effective for time horizons $<$ 5 years and nearly cost-effective at 5 years (ICER $118,324). One-way sensitivity analysis revealed that SIC became cost-effective relative to RCx if its risk of recurrence or metastasis at 2 years was less than 55% or 5.9%, respectively. For index patient 2, pembrolizumab required $>$ 90% price reduction to be cost-effective vs. RCx (ICER $1,073,240). Probabilistic sensitivity analyses revealed that pembrolizumab was unlikely to be cost-effective even at high willingness-to-pay thresholds. Further sensitivity analyses found that no two-way combination of extrapolated values resulted in pembrolizumab being favored over RCx or SIC for either index patient. **Conclusions:** Based on decision-analytic Markov modeling of treatment options for patients with BCG-unresponsive CIS, pembrolizumab was unlikely to be cost-effective without a $>$ 90% price reduction. While both RCx and SIC were more cost-effective than pembrolizumab, further studies may validate the cost-effectiveness of gemcitabine-docetaxel relative to RCx if the recurrence and metastasis thresholds are met. Overall, our model supports the preferential use of RCx and SIC over pembrolizumab for BCG-unresponsive CIS. Research Sponsor: VA Health Services Research and Development Fellowship Program supported Vidit Sharma.

Phase II study of gemcitabine and split-dose cisplatin plus pembrolizumab as neoadjuvant therapy prior to radical cystectomy (RC) in patients with muscle-invasive bladder cancer (MIBC).

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Background: Cisplatin-based neoadjuvant chemotherapy is standard of care in MIBC with improved pathologic response and overall survival (OS) compared to RC alone. Pembrolizumab (pembro) is active in high-risk non-muscle invasive and metastatic bladder cancer and is generally well tolerated. This phase II trial evaluated the safety and efficacy of gemcitabine and split-dose cisplatin (GC) + pembro as neoadjuvant therapy prior to RC (NCT02690558). **Methods:** Patients with clinical T2-4a N0/X M0 urothelial carcinoma of the bladder eligible for RC were enrolled. Patients received pembro 200mg on day 1 with cisplatin 35mg/m^2 and gemcitabine 1000mg/m^2 on days 1 and 8 every 3 weeks for 4 cycles, followed by RC within 4-8 weeks. The first 6 patients received full-dose cisplatin (70mg/m^2 on day 1) and a lead-in pembro dose; this schedule was discontinued for excess toxicity. Primary endpoint was pathologic downstaging rate ($<$ pT2) with the null and alternative hypothesis rates = 35% and 55%, respectively. Secondary endpoints were toxicity, pT0 rate, event free survival, and OS. Exploratory objectives include association of response with molecular subtype and post-treatment changes in immune microenvironment (predicted neoantigens, immune gene expression, and T cell receptor repertoire). **Results:** Between May 2016 and July 2020, 39 patients were enrolled (72% cT2, 23% cT3, 5% cT4a) with a median age of 66 and 82% male. Patients received a median of 4 cycles of therapy. All patients underwent RC except one who declined but is included in intention to treat analysis. Rate of $<$ pT2N0 was 56% (22/39) and pT0N0 rate was 36% (14/39). Most common adverse events (AEs) of any grade were thrombocytopenia (29/39; 74%), anemia (27/39; 69%), neutropenia (26/39; 67%), and hypomagnesemia (26/39; 67%). Most common grade 3/4 AEs were neutropenia (16/39; 41%), thrombocytopenia (13/39; 33%), febrile neutropenia (5/39; 13%), and anemia (4/39; 10%). One patient had new onset type 1 diabetes mellitus with ketoacidosis related to pembrolizumab and no patients required steroids for immune-related AEs. Nine patients (23%) discontinued GC + pembro due to AEs, including 4 of the 6 patients who received full-dose cisplatin with pembro lead-in. Survival data are not yet mature and correlative studies are ongoing. **Conclusions:** Neoadjuvant GC + pembro was generally safe and met its primary endpoint for improved pathologic downstaging. Correlative analyses are ongoing. Additional investigation of this combination is warranted. Clinical trial information: NCT02690558. Research Sponsor: Merck, U.S. National Institutes of Health.

397 **Rapid Abstract Session**

A phase II trial of risk enabled therapy after initiating neoadjuvant chemotherapy for bladder cancer (RETAIN BLADDER): Interim analysis.

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Background: Cisplatin-based neoadjuvant chemotherapy (NAC) followed by cystectomy (Cx) or chemoradiation (CRT) is the standard of care for urothelial carcinoma (UC) pts with muscle invasive bladder cancer (MIBC). Both Cx and CRT have potential short and long-term toxicity and QOL implications. Mutations in DNA damage repair/response genes are associated with pathologic downstaging after NAC. **Methods:** We conducted a phase II, multi-institutional clinical trial (NCT02710734) to evaluate a risk-adapted approach to treatment of MIBC. Pts with cT2-T3N0M0 UC of the bladder, ECOG PS 0-1 and CrCl≥50 mL/min, underwent NAC with accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC). Pre-NAC TURBT specimens were sequenced (Caris Life Sciences) for mutations (pathogenic or VUS) in *ATM*, *ERCC2, FANCC or RB1*. Pts with at least one mutation and no clinical evidence of disease by restaging TUR and imaging post-NAC began pre-defined active surveillance (AS). Remaining pts underwent bladder-directed therapy: intravesical therapy (< cT2 post-NAC), CRT or Cx. The primary endpoint was metastasis-free survival (MFS) at 2 years which is not mature. We herein report key interim results of clinically-meaningful intermediate endpoints. **Results:** Seventy-one (ITT) pts were enrolled over 33 months at four academic centers. Median age was 70 years (47-83), 74% were male, 92% Caucasian, 81% ECOG PS 0 and 79% cT2. 90% completed 3 cycles of NAC and with 17% grade 3-4 TRAEs and one death during AMVAC. At the time of data cut-off (September 11, 2020), for the ITT pts, 32 pts have had a Cx, 5 underwent CRT and 7 underwent intravesical therapy, at some point during the trial. Thirty-three pts (46%) had a mutation of interest and 28 pts (39%) started AS (2 of the 28 pts on AS did not have a mutation but elected to start AS after achieving cT0 post AMVAC). 76% of those with a mutation were cT0 at post-NAC TURBT. With a median follow-up of 14.9 mo (range: 3.1-35.3 mo), 14 AS pts recurred (50%). Of the 14 recurrences, 2 recurred with locally advanced or metastatic disease and have died, 5 had MIBC with one eventual metastatic recurrence, and 7 had NMIBC. Six (14%) non-AS pts have died. Out of the 40 pts who did not go to upfront Cx [AS (N = 28), CRT (N = 5), intravesical tx (N = 7)], 3 (7.5%) (all in the AS group) went on to Cx later. The bladder preservation rate is 55% for ITT pts and 89% for the AS group. In the AS cohort, mutations were seen in *RB1* (50%), *ATM* (42%), *ERCC2* (31%), *FANCC* (4%) with lowest rate for recurrence in *ERCC2* (25% recurrence) vs *RB1* (62% recurrence). **Conclusions:** Interim results of a phase II trial of risk enabled therapy utilizing a selection of clinical and genomic factors in pts with cT2-T3 MIBC demonstrates a 50% rate of any UC recurrence and a 11% rate of locally advanced/metastatic disease in the AS group. 89% of AS pts have retained their bladder. Follow-up continues for the primary endpoint of 2-year MFS. Clinical trial information: NCT02710734. Research Sponsor: Fox Chase Cancer Center.

Phase II clinical study of concurrent durvalumab and radiation therapy (DUART) followed by adjuvant durvalumab in patients with localized urothelial cancer of bladder: Results for primary analyses and survival. BTCRC-GU15-023.

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Background: Bladder cancer (BC) patients (pts) who are cisplatin ineligible/unfit for surgery, or locally advanced and unresectable have limited treatment options. DUART investigates if the combination of radiation therapy (RT) and checkpoint inhibitor, durvalumab (durva) is safe and effective in these pts. We recently reported that the combination was safe, tolerable and disease control rate (DCR) was 92% post durvaRT. Here we present interim efficacy data of our phase II study. **Methods:** Pts with pure or mixed urothelial bladder cancer (T2-4 N0-2 M0) were enrolled if their tumor was unresectable (35%), were unfit for surgery (50%) and/or cisplatin ineligible (89%). Primary endpoints: a) PFS at 1-yr b) DCR post adjuvant durva; Secondary endpoints: a) CR post durvaRT b) median PFS c) median OS. Pts were treated with durva (1500mg) Q4 wks x2 doses along with definitive RT (64.8Gy, 36 fractions over 7 wks) to the bladder and involved nodes followed by adjuvant durva Q4 wks x 1 yr. Response was evaluated with CT scan and cystoscopy+biopsy. Sample size was based on assumption that this regimen would increase 1 yr PFS by 25% compared to RT alone (50% to 75%); we assumed DCR of 75%. A total of 26 pts were needed to reach a statistical power of at least 80% at one-sided alpha of 5% and to allow for 10% drop out rate. **Results:** Twenty-six pts (19 males, 7 females) were enrolled, median age 74 yr (51-94). Sixty two percent of pts had >T2 disease, 31% had positive lymph nodes; 62% with unresectable tumor or were unfit for surgery due to comorbidities. At data cut off (9/30/2020) 20/26 pts were evaluable for DCR post adjuvant durva (3 pts with CR post durvaRT, did not get adjuvant therapy; 1 pt withdrew after 3 cycles for adjuvant durva and was on f/u with unconfirmed CR; 2 pts are still on adjuvant durva) and 25/26 for PFS and all 26 pts for OS. Post completion of adjuvant durva, DCR was seen in 70 % (14/20 with 10 CR; 3 PR; 1 SD; 6 PD). One-year probability of PFS was 73% (95% CI 56.4%, 94.4%), median PFS was 18.5 months. One-year OS probability was 83.8% (95% CI 70.4%, 99.7%) with two-year OS probability of 76.8 (95% CI 60.2%, 98%). Median OS has not been reached. We did not observe any correlation between clinical outcome and baseline tumor PD-L1 expression. **Conclusions:** DurvaRT followed by adjuvant durva demonstrated promising efficacy with 1-year PFS probability of 73%, 1- year OS probability of 83.8% and DCR of 70% in MIBC and locally advanced BC pts with comorbidities. Results will be updated prior to the final presentation. Efficacy was also seen in node (+) pts which led to the design of prospective randomized NCTN study. Induction chemo followed by chemo+durvaRT+ adjuvant durva vs. chemoRT combination is being evaluated in the ongoing EA8185 clinical trial (ECOG-ACRIN/NRG study) for node (+) BC pts. Clinical trial information: NCT02891161. Research Sponsor: AstraZeneca.

Impact of equal access healthcare on race disparities in bladder cancer.

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Background: Outcomes in bladder cancer are disproportionately worse for black patients compared to white patients. We hypothesize these disparities arise in part due to differences in access to healthcare and therefore may be mitigated in an equal access healthcare system, such as the Veterans Affairs' (VA) system. Here, we examine outcomes by race for patients with bladder cancer within the VA system and then compare these outcomes to those in the Surveillance, Epidemiology, and End Results (SEER) database. **Methods:** We performed a retrospective cohort study using VA Informatics and Computing Infrastructure (VINCI) and SEER. We included all patients diagnosed with bladder cancer, American Joint Committee on Cancer (AJCC) stage 0-4 diagnosed between 2000 and 2018. Endpoints of overall survival (OS), bladder cancer-specific survival (BCS), and non-bladder cancer-specific survival (NCS) were evaluated in multivariable Cox and Fine-Gray models. **Results:** Using the VA dataset, we identified 36322 veterans (9.0% black, 91.0% white) with bladder cancer. Black veterans were more likely to have more comorbidities, reside in zip codes with lower median income and education levels, and present with higher stage disease (AJCC stages 2-4) than white veterans (23.3% vs 19%). In multivariable models accounting for disease stage among other covariables, there were no statistically significant differences in any survival endpoint (Table). Using the SEER dataset, we identified 130998 patients (5.9% black, 94.1% white) with bladder cancer. In similar multivariable models, SEER's black patients had statistically significant inferior outcomes in all survival endpoints compared to SEER's white patients (Table). **Conclusions:** While racial disparities for patients with bladder cancer in the SEER database were observed, no differences in survival outcomes between black and white patients were observed in the VA healthcare system. Of note, black veterans presented with more advanced stage, suggesting a delay in diagnosis or a more aggressive cancer phenotype compared to white patients. Our findings underscore the need to bridge healthcare disparities across diverse racial groups. Our study highlights the beneficial impact of an equal access healthcare system in reducing financial and social barriers to healthcare to counteract racial health disparities. Further research is required to delineate these disparities and guide appropriate screening strategies. Research Sponsor: U.S. National Institutes of Health.

Summary of race (Black vs White) hazard ratios in multivariable models in VA dataset compared to SEER dataset.

	Race Black vs White Hazard Ratios			
	VA Dataset		SEER Dataset	
Survival Endpoints	HR (95% CI)	P value	HR (95% CI)	P value
Overall Survival	1.00 (0.94-1.07)	0.89	1.32 (1.28-1.38)	< 0.0001*
Bladder Cancer-Specific Survival	1.01 (0.92-1.10)	0.90	1.31 (1.26-1.38)	< 0.0001*
Non-Bladder Cancer-Specific Survival	0.96 (0.90-1.04)	0.32	1.18 (1.12-1.25)	< 0.0001*

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Racial differences in aneuploidy in high-grade muscle-invasive bladder cancer.

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Background: Bladder cancer is marked by racial disparities in stage at presentation, treatment, and survival. It is unknown how somatic tumor genomes differ by race. Tumor aneuploidy, defined as aberrant counts of chromosome arms, is pervasive in tumors including bladder cancer. Its associations with race are incompletely understood. We sought here to characterize the relation of race with aneuploidy in high-grade muscle-invasive bladder cancer. **Methods:** To quantify how aneuploidy differs by race, we leveraged the cohort of patients with high-grade, muscle-invasive bladder cancer from The Cancer Genome Atlas. Chromosome arm gains and losses were identified based on Affymetrix SNP 6.0 arrays (Taylor 2018). We focused on aneuploidy burden defined as the count of chromosome arms altered by gains and losses per tumor, which was based on both p and q chromosome arms of all autosomes except for acrocentric autosomes (q arms only) and ranged from 0 to 34 altered chromosome arms. We used multivariable linear regression to obtain mean differences and 95% confidence intervals (CIs) in the number of altered chromosome arms between self-reported racial groups, adjusting for demographics (sex, age at diagnosis, smoking status) and tumor characteristics (grade, histology). We also evaluated associations between race and number of altered chromosome arms stratified by papillary/non-papillary histology and sex. **Results:** Of 362 participants, 315 self-identified as White (87%), 25 as Asian (7%), and 22 as Black (6%). 73% were men, 21% were current smokers, and 52% former smokers. Median age at diagnosis was 69 years (interquartile range [IQR]: 61 to 76). Asians and Blacks tended to be younger at diagnosis than Whites, with more never-smokers among Asians. More profiled tumors were of papillary histology among Asians (44%), and fewer among Blacks (18%), than among Whites (30%). Aneuploidy burden was high overall (median, 14 altered chromosome arms; IQR: 8 to 19); only 17% of tumors had five or fewer altered chromosome arms. Compared to Whites, aneuploidy burden overall was similar in tumors from Asians (adjusted mean difference, −2.3 fewer altered chromosome arms; 95% CI: −5.4 to 0.9) and Blacks (−1.7; 95% CI: −5.1 to 1.7). Asian race appeared more strongly associated with lower aneuploidy burden in non-papillary tumors (−3.9 altered chromosome arms; 95% CI: −7.7 to −0.1) than in papillary tumors (−0.3; 95% CI: −5.6 to 5.0), and in men (−3.5; 95% CI: −7.0 to 0.1) than in women (−0.8; 95% CI: −6.8 to 5.2). **Conclusions:** These findings suggest potential differences in aneuploidy burden between Asians and Whites among high-grade muscle-invasive bladder cancers. They also highlight a need for validation in cohorts that are more racially diverse and have a well-defined source population (study base) with detailed data on cancer risk factors and histopathology. Research Sponsor: Harvard–MIT Bridge Project.

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A multicenter, retrospective study on impact of immunotherapy in urothelial carcinoma with bone metastases (Meet-Uro01 Study).

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Background: Considerable numbers of patients (pts) with metastatic urothelial carcinoma (mUC) (approximately 25-47%) develop bone metastases (BoM). Their impact on the efficacy of immunotherapy (IO) is not yet sufficiently investigated. We developed a national collaboration on this issue, with the aim to assess the effect of BoM on survival outcomes of immunotherapy-treated pts in a large retrospective cohort. **Methods:** Data on pts diagnosed with mUC and treated between 07/14 and 08/20 with single-agent immunotherapy (IO) after failure of at least 1 previous line of chemotherapy (CT) for advanced disease, or (neo-)adjuvant CT within 12 months were retrospectively collected across 14 centers. PFS and OS were analyzed using the Kaplan-Meier method. Cox regression analysis was performed evaluating potential prognostic factors for OS and PFS. Each factor was evaluated in univariable (UV) and multivariable (MVA) analysis. **Results:** A total of 208 evaluable pts treated with single-agent immunotherapy (anti PD-1 n=42; anti PD-L1 n=166) were identified, including 122 without BoM (59% BoM-) and 86 (41%) BoM+. 13% of pts had progressed within 12 months after (neo-)adjuvant CT and 79% after a previous line of platinum-based CT for advanced disease (cisplatin 42.8%; carboplatin 36.5%). The presence of BoM negatively affected performance status (PS) of patients at baseline (ECOG PS 0/1/2 in 58% / 37% / 5% in BoM- vs 38% / 52% / 9% in BoM+; p=0.017). Other baseline characteristics were comparable. BoM+ showed shorter PFS (median 2.0 *vs* 2.6 months, HR 1.76 [95%CI, 1.31-2.37], p<0.001) and OS (median 3.9 *vs* 7.8 months, HR 1.59 [95%CI, 1.15-2.20], p=0.005) than BoM-. Probability of being alive was 62% vs 40% after 6 months, 38% vs 23% after 1 year and 24% vs 13% after 2 years, in BoM- and BoM+ respectively. Within each Bellmunt score, PFS and OS of BoM+ pts were shorter compared to BoM-. Both BoM and higher Bellmunt risk score were significantly associated with shorter PFS and OS in UV and MV analyses (Table). **Conclusions:** Patients with mUC treated with single-agent immunotherapy for BoM+ advanced disease have a dismal prognosis compared with BoM-. Further research is needed to understand the mechanism behind these clinical outcomes. Research Sponsor: None.

Progression-free survival multivariable analysis (n=157 patients).

Covariate		Hazard Ratio (95%CI)	P value
Bone metastases	Yes *vs* no	1.764 (1.244 - 2.500)	0.001
Bellmunt score	1 *vs* 0	1.715 (1.163 - 2.529)	0.004
	2-3 *vs* 0	2.102 (1.294 - 3.417)	
Overall Survival Multivariable analysis (n=157 patients)			
Covariate		**Hazard Ratio (95%CI)**	**P value**
Bone metastases	Yes *vs* no	1.790 (1.245 - 2.572)	0.002
Bellmunt score	1 *vs* 0	1.873 (1.245 - 2.818)	<0.001
	2-3 *vs* 0	2.795 (1.667 - 4.689)	

Do females have worse surgical outcomes after radical cystectomy? Impact of gender on 30-day complications in a national cohort.

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Background:: Men have higher rates of bladder cancer and are more likely to undergo cystectomy than women, yet women seem to have worse oncologic outcomes. This is attributed to biologic factors including adverse histologic variants and social factors including delay in diagnosis. There is early evidence that women also have worse surgical outcomes. We further examined the role of gender in 30-day perioperative outcomes following radical cystectomies in a national cohort. **Methods:** We examined the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) from 2012 to 2016. The database was searched for CPT codes reflecting radical cystectomy and a diagnosis of "cancer of the bladder." Frailty was estimated by the modified frailty index (functional status, diabetes, chronic obstructive pulmonary disorder, history of chronic heart failure, and hypertension requiring medication.) To compare demographic and perioperative characteristics between genders, Chi-Square analyses were performed for categorical variables, student's t test to compare averages, and the Wilcoxon rank sum test for operative time and length of stay (LOS). **Results:** 4,681 radical cystectomies were identified including 842 (18.0%) females. Of the female cohort, average age was 68.6 (+/-11.2 years), 77.3% was Caucasian and 278 (33%) had a BMI of at least 30. There were no differences appreciated between genders with regards to age, average ASA score, frailty, or minimally-invasive approach (all p=NS). Compared to males, female gender was associated with longer operative time (350 vs. 336 min, $p<0.009$), length of stay (LOS) (8 vs 7, $p<0.001$) and lower rates of discharge to home (79.9% vs 87.0%, $p<0.0001$). Reoperation (4.8% vs. 6.0%), readmission (22.2% vs 20.6%), and death within 30 days (1.9% vs. 2.0%) were similar. Clavien 3 or greater was also similar among gender (Table). **Conclusions:** Female patients comprise a minority of radical cystectomies with slightly longer LOS and less home discharge than men, yet 30-day major complications, reoperation and mortality appear similar. Research Sponsor: None.

Comparison of 30-day perioperative outcomes between females and males.

Variable	Level	Female	Male	p-value
Death	Yes	16 (1.9%)	77 (2.01%)	0.8467
Reoperation	Yes	40 (4.76%)	229 (5.96%)	0.173
Readmission	Yes	187 (22.24%)	791 (20.6%)	0.2904
Discharged Home	Yes	672 (79.9%)	3339 (86.95%)	<0.0001*
Clavien Dindo	0	259 (30.8%)	1798 (46.82%)	<0.0001*
	1-2	442 (52.55%)	1408 (36.67%)	
	3-5	140 (16.64%)	634 (16.51%)	
Total Hosp. Length of Stay median (25^{th}-75^{th} percentile)		8 (6 - 11)	7 (6 - 10)	0.0007*
Total Operation Time median (25^{th}-75^{th} percentile)		350 (275 - 434)	336 (263 - 422)	0.0096*

Social disparities in the diagnosis and management of bladder cancer.

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Background: The socioeconomic characteristics associated with the diagnosis and management of bladder cancer are not well described. **Methods:** We utilized the National Cancer Database (NCDB) to stratify cases of urothelial cell carcinoma of the bladder by the National Comprehensive Cancer Network (NCCCN) guidelines: early (Tis, Ta, T1), muscle invasive (T2-T3, N0), locally advanced (T4, N1-3), and metastatic. We then used multivariate binomial and multinomial logistic regression analyses to identify demographic characteristics associated with stage at diagnosis and receipt of cancer-directed therapies. Hazard ratios (HR) are reported with 95% confidence intervals. **Results:** After exclusions, we identified 331,714 early, 72,154 muscle invasive, 15,579 locally advanced, and 15,161 metastatic cases. Relative to diagnosis at early stage, the two strongest independent predictors of diagnosis at muscle invasive, locally advanced, and metastatic disease included black race (HR = 1.19 [1.15-1.23], HR = 1.49 [1.40-1.59], HR = 1.66 [1.56-1.76], respectively), and female gender (HR = 1.21 [1.18-1.21], HR = 1.16 [1.12-1.20], and HR = 1.34 [1.29-1.38], respectively). Additional demographic factors associated with diagnosis at a more advanced stage on multivariable analysis included older age, treatment at an academic center (except for metastasis), Medicaid insurance, and patients from lower income/ less educated/more rural areas (all $p < 0.01$). The following demographic factors were less likely to receive cancer-directed therapies, signified by odds ratios, per multivariable binomial regression analysis: Additionalyl, female patients (HR = 1.03, 1.02-1.05) and black patients (HR = 1.13, 1.11-1.16) were the only demographic correlates of reduced survival in the entire cohort with multivariable cox regression analysis. **Conclusions:** In the largest study of its kind, we report that several socioeconomic, racial, and gender factors are associated with the diagnosis of bladder cancer at a later stage, as well as the use of less cancer-directed treatments. Further investigation is warranted to better characterize, and ultimately improve upon, health disparities in bladder cancer. Research Sponsor: None.

Parameter	Early stage	Muscle invasive	Locally Advanced	Metastatic
Non-academic center	0.53 (0.49-0.59)	0.56 (0.41-0.77)	NS	NS
Age (continuous)	0.98 (0.98-0.99)	0.96 (0.95-0.97)	0.96 (0.95-0.97)	0.97 (0.96-0.98)
Female	0.87 (0.83-0.92)	0.83 (0.70-0.98)	0.74 (0.61-0.89)	0.88 (0.78-0.99)
Hispanic	0.85 (0.74-0.97)	NS	NS	0.73 (0.55-0.97)
Lower income area	0.82(0.75-0.89)	0.73 (0.57-0.93)	NS	NS
Rural area	0.75 (0.65-0.86)	NS	NS	NS
Black race	0.67 (0.61-0.74)	0.51 (0.39-0.66)	0.64 (0.48-0.86)	0.78 (0.65-0.95)

Is there a role for urine cytology following BCG therapy for non-muscle-invasive bladder cancer (NMIBC)?

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Background: Voided urine cytology has been used as an adjunct in the diagnosis of non-muscle invasive bladder cancer (NMIBC), with a sensitivity and specificity ranging between 13-75% and 76-100% respectively. There is limited data on the accuracy and utility of cytology following BCG therapy. We reviewed the results of cytology in patients undergoing induction and maintenance BCG immunotherapy in our institution. **Methods:** Newly diagnosed patients who had received induction and maintenance intravesical BCG therapy from 2004 - 2019 were identified from a prospective database and their outcomes reviewed retrospectively. Histopathology results of biopsies / resected specimens and voided urine cytology results were examined for 273 patients. **Results:** A total of 2567 cytology results and 638 biopsy results were recorded. The average age was 73.2 years and median number of BCG treatments was four (induction followed by three maintenance courses). Median follow up was 38 months. 94 patients (34.4%) had recurrence following BCG therapy. Of those 33 patients (12.1%) had progression to muscle invasive disease. The number of cytology samples per patient after BCG therapy ranged from 1-23 (median 7), with several patients having repeated, potentially unnecessary negative urine cytology. Overall accuracy of cytology (n = 526) was sensitivity 44.2%, specificity 84.7%, PPV 38.9%, NPV 87.3%. Patients that had an erythematous bladder or red patch at flexible cystoscopy underwent subgroup analysis; this gave a very high NPV of 95.9%, with additional sensitivity being 65.5%, specificity 85.9% and PPV 33.3%. Number of positive cytology results (Chi^2 = 44.30, P = 0.002), any positive cytology (Chi^2 = 27.94, $P < 0.001$) and positive cytology after induction BCG therapy (Chi^2 = 30.381, $P < 0.001$) were all strongly associated with recurrence. **Conclusions:** Positive urine cytology in patients undergoing intravesical BCG therapy predicts increased risk of recurrence and has good specificity. We would recommend using voided urine cytology in patients who have an erythematous bladder or red patch at flexible cystoscopy. If the cytology is positive then proceed to biopsy, however, if it is negative continue with surveillance. Research Sponsor: None.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Cytology after induction BCG with biopsy confirmation (n = 231)	46.3%	90%	50%	88.6%
Cytology after induction BCG, including negative cystoscopy +/- biopsy (n = 273)	46.3%	87.6%	39.6%	90.3%
Cytology at any other time with biopsy confirmation (n = 253)	42.6%	81.4%	38.3%	83.9%
All cytology including negative cystoscopy +/- biopsy (n = 526)	44.2%	84.7%	38.9%	87.3%

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Does the diagnostic modality for upper tract urothelial carcinoma prior to radical nephroureterectomy influence the risk of subsequent intravesical recurrence?

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Background: The diagnosis of upper tract urothelial carcinoma (UTUC) is frequently obtained via diagnostic ureteroscopy (URS) with biopsy. In a recent meta-analysis of five retrospective series comparing UTUC RNU patients with and without prior diagnostic URS, prior URS was associated with intravesical recurrence of urothelial carcinoma. However, there remains an incomplete understanding of the risks of URS on intravesical recurrence after RNU, and existing studies have not examined the risks of URS without endoscopic biopsy or percutaneous biopsy alone. Here, we query our institutional RNU registry to determine if UTUC diagnostic modality influences post-RNU intravesical recurrence risk. **Methods:** Years 1995 to 2019 of our institutions RNU registry were queried. Patients with UTUC were divided into four groups: 1) URS with endoscopic biopsy; 2) URS without endoscopic biopsy (visual confirmation alone); 3) percutaneous biopsy without any URS; 4) no URS and no percutaneous biopsy. Exclusion criteria included pure non-urothelial histology, RNU for benign indications, and prior/concomitant cystectomy. The primary outcome was intravesical recurrence of urothelial carcinoma compared across the four groups using Kaplan-Meier log-rank analyses and Cox-proportional hazard modeling (hazard ratio = HR). **Results:** In a cohort of 878 patients (mean post-RNU follow-up 43 months), 461 (53%) had URS with biopsy, 130 (15%) had URS without biopsy, 229 (26%) had no URS or percutaneous biopsy, and 58 (7%) had percutaneous biopsy alone. The 3-year intravesical recurrence rate was 27%, 22%, 18%, 12% for groups 1-4, respectively. Covariates associated with intravesical recurrence on univariable analysis included age (HR 1.03, $p < 0.01$), female gender (HR 0.76, $p = 0.06$), history of bladder cancer (HR 1.39, $p = 0.01$), current smoker (HR 1.49, $p = 0.04$), and multifocality (HR 1.34, $p = 0.03$). After adjusting for these covariates, multivariable analysis found that group 1 (URS with biopsy) was associated with increased intravesical recurrence (HR 1.41, $p = 0.03$) relative to group 3 (no URS or percutaneous biopsy). Compared to group 1, the hazard ratio for intravesical recurrence was not significantly different for group 2 (HR 1.18, $p = 0.45$) or group 4 (HR 1.11, $p = 0.79$). **Conclusions:** Patients undergoing ureteroscopic biopsy to diagnose UTUC prior to RNU had a higher risk of intravesical recurrence after RNU compared to patients who did not undergo any URS or percutaneous biopsy. This agrees with prior literature and suggests that aggressive ureteroscopic manipulation of UTUC tumors via biopsy may promote shedding of urothelial carcinoma cells capable of seeding the bladder. Our study does support the initiation of a randomized trial to determine if intravesical chemotherapy after ureteroscopic biopsy can reduce intravesical urothelial carcinoma recurrences. Research Sponsor: None.

Immune checkpoint inhibitors (ICI) in advanced upper tract and lower tract urothelial carcinoma (UC): A comparison of outcomes.

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Background: Despite anatomical and biological differences, upper and lower tract UC (UTUC; LTUC) are usually managed similarly. Modern era clinical trial data comparing their outcomes with ICI are conflicting. We hypothesized that response and outcomes would be similar in patients (pts) with advanced UTUC and LTUC. **Methods:** We performed a retrospective cohort study collecting demographic, clinicopathologic, treatment, and outcome data for pts with advanced UC receiving ICI (2013-2020) across 24 centers (US; Europe). We compared objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) between pts with UTUC and LTUC. Uni- / multi- variable logistic and Cox regression were used to assess the effect of UTUC on ORR, OS, and PFS. Stratified subgroup analyses were performed according to histology (pure, mixed) and line of treatment (first-line, subsequent). **Results:** A total of 984 pts were identified, and 707, 717, and 738 were included in ORR, OS, and PFS analyses, respectively. After exclusions, the UTUC group comprised of 130 pts (vs. 616 in LTUC) with median age 71 (40-92) (vs. 70 [32-93]), 62% men (vs. 76%), 41% never smokers (vs. 29%), 62% with history of prior radical surgery for primary tumor (vs. 52%), and 29% with liver metastases (vs. 18%). Table shows results of ORR, OS, and PFS analyses. In the overall population, pts with UTUC and LTUC receiving ICI had comparable ORR, OS, and PFS. Pts with mixed-histology UTUC had significantly lower ORR (adjusted OR 0.20, 95%CI 0.05-0.91) and shorter PFS (adjusted HR 1.66, 95%CI: 1.06-2.59) vs. mixed-histology LTUC. **Conclusions:** Pts with advanced UTUC and LTUC receiving ICI have similar response and outcomes, except for pts with mixed-histology UTUC vs LTUC. Subset analysis of primary tumor location in ongoing clinical trials can validate our data, while biomarker work is ongoing. Research Sponsor: None.

	N	ORR (%) (95%CI)	OR (95% CI)	N	Median OS (months)	HR (95% CI)	N	Median PFS (months)	HR (95% CI)
LTUC	584	28 (25-32)	Ref.	590	9.6 (8.2-11.4)	Ref.	609	4.1 (3.5-4.9)	Ref.
UTUC	123	24 (18-33)	0.73 (0.43-1.24)	127	9.8 (7.9-14.3)	0.93 (0.73-1.19)	129	4.3 (3.2-5.9)	1.01 (0.81-1.27)
Pure LTUC	414	28 (24-33)	Ref.	417	9.3 (7.8-11.4)	Ref.	431	4.1 (3.4-4.9)	Ref.
Pure UTUC	95	28 (20-38)	1.00 (0.56-1.78)	98	10.9 (8.3-14.4)	0.83 (0.62-1.10)	99	4.6 (3.3-6.9)	0.87 (0.67-1.13)
Mixed LTUC	170	29 (23-37)	Ref.	173	10.6 (6.7-14.1)	Ref.	178	4.3 (3.0-7.4)	Ref.
Mixed UTUC	28	11 (4-29)	0.20 (0.05-0.91)	29	7.6 (2.4-19.1)	1.36 (0.85-2.17)	30	2.2 (1.6-5.9)	1.66 (1.06-2.59)
First-line LTUC	328	31 (26-36)	Ref.	339	10.9 (7.9-13.2)	Ref.	347	4.6 (3.5-6.3)	Ref.
First-line UTUC	57	35 (24-48)	1.17 (0.58-2.37)	62	13.4 (8.3-19.9)	0.85 (0.58-1.24)	62	4.6 (2.5-8.3)	1.01 (0.73-1.41)
Subsequent LTUC	256	26 (21-32)	Ref.	251	8.6 (7.3-10.9)	Ref.	262	3.7 (3.0-4.4)	Ref.
Subsequent UTUC	66	15 (8-26)	0.51 (0.22-1.20)	65	8.4 (5.3-14.0)	1.05 (0.75-1.46)	67	4.1 (2.8-5.9)	1.07 (0.79-1.47)

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Approaches to immune checkpoint inhibitor (ICI) maintenance therapy in metastatic urothelial cancer (mUC): A qualitative analysis of oncology providers in the United States.

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Background: Avelumab first-line (1L) maintenance therapy for patients (pts) with advanced/mUC that has not progressed with platinum-containing chemotherapy was recently approved in the US based on improved overall survival seen in the JAVELIN Bladder 100 trial. However, provider perspectives regarding 1L maintenance therapy in mUC have not been reported. **Methods:** We performed a qualitative interview study with US oncologists and oncology nurses treating pts with mUC in academic and community practices. Telephone interviews were conducted in August 2020 using a semi-structured discussion guide to explore decision-making processes about treatment for pts with mUC and perspectives about ICI maintenance therapy in the 1L setting. The latter was defined as either 1) ICI for pts who achieve disease control with platinum-containing chemotherapy (Regimen A) or 2) ICI + chemotherapy followed by ICI (Regimen B). Thematic analysis identified key determinants and clinical considerations associated with ICI maintenance therapy in mUC. **Results:** Results for 18 oncologists (mean age 51.3 yrs [SD 9]; 11% female; 55% with >15 yrs in practice; 39% academic) and 18 oncology nurses (mean age 43.8 yrs [SD 11.1]; 94% female; 34% with >15 yrs in practice; 50% academic) are reported. Cisplatin- and carboplatin-based chemotherapy regimens were the most commonly administered 1L treatments, with ICI monotherapy reserved only for frail (i.e., comorbid and/or elderly) pts. All oncologists recommended 4-6 cycles of 1L chemotherapy. Providers reported different perspectives about the maintenance approaches. Those who expressed a preference for Regimen A (oncologists, 66.6%; nurses, 71.4%) cited potentially less toxicity as a key factor driving their choice. Providers who preferred Regimen B cited the perceived potential for deeper and more durable responses based on previous experience with this maintenance approach in other tumors as a driver of their choice. For Regimen A, providers universally did not recommend a treatment break between chemotherapy and ICI maintenance because of concerns about progression. Frequency of administration was not cited as a driver of treatment decisions for either maintenance approach; instead, providers prioritized survival and tolerability. Responses were generally consistent between oncologists and nurses. **Conclusions:** Overall, providers adhered to new guidelines for 1L treatment of mUC (NCCN and ESMO) and expressed receptivity toward Regimen A. Although few providers had experience with this new regimen, most preferred it vs ICI + chemotherapy followed by ICI in 1L mUC. Our findings highlight the need to increase provider awareness of Regimen A, i.e., avelumab maintenance in pts with response or stable disease with 1L chemotherapy as a standard of care in advanced/mUC, which has Level I evidence. Research Sponsor: Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer.

Reliability, validity, and clinically important differences (CIDs) on the NCCN/FACT Bladder Symptom Index (NFBISI-18) among individuals with locally advanced or metastatic urothelial cancer (UC).

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Background: The NFBISI-18 is a measure of advanced bladder cancer–specific symptoms composed of a total scale and 3 subscales representing physical disease–related symptoms (DRS-P), emotional disease–related symptoms (DRS-E), treatment side effects (TSE), and function/well-being (F/WB). There is evidence for the reliability and content validity of this instrument, but a full psychometric evaluation of the full 18-item format has not been done. In addition, CIDs have not been estimated. **Methods:** With the exception of test-retest (TRT) analyses, baseline data (n=651) from the JAVELIN Bladder 100 trial (NCT02603432), which compared maintenance treatment with avelumab + best supportive care (BSC) vs BSC alone in patients with unresectable, locally advanced or metastatic UC that did not progress with first-line platinum-containing chemotherapy, were used for this study. Since we focused on baseline, we did not analyze the TSE. We estimated internal consistency reliability (Cronbach coefficient α), tested convergent validity by estimating Spearman ρ correlations with the EQ-5D-5L utility index (UI) and visual analog score (VAS) scales, and estimated known group validity using age ($<$65, $\geq$65 years), ECOG performance status rating (PSR), and number of comorbidities/symptoms (1-9, $\geq$10) as anchors. We estimated TRT reliability using data from treatment cycles 2-3 with intraclass correlation coefficients (ICCs). To estimate and compare CIDs, we calculated differences in means between categories of the known group anchors for which Cohen's *d* was $>$0.2 (ie, at least a small effect). To provide context for the CIDs, we calculated distributional properties of the scales (1/2 standard deviation [SD], 1 standard error of measurement [SEM]). **Results:** The table shows the reliability, convergent validity, and CID estimates. Reliability estimates often exceeded thresholds for reliability generally considered acceptable. Cohen's *d* for NFBISI-18 scale score differences between known groups ranged between 0.05 and 0.25 (age), 0.35 and 0.6 (ECOG PSR 0 vs 1), and 0.1 and 0.41 (number of comorbidities/symptoms). **Conclusions:** This analysis demonstrated that the NFBISI-18 is a reliable and valid instrument to measure symptoms in patients with advanced UC. The CID estimates can help clinicians and researchers to understand what difference in patient symptoms are clinically meaningful, as measured by NFBISI-18, to inform clinical practice. Research Sponsor: Pfizer, as part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.

NFBISI-18 scale	Internal consistency (α)	TRT reliability (ICC)	Spearman ρ with EQ-5D-5L		Score range	CID estimate	Distribution estimates	
			UI	VAS			0.5 SD	1 SEM
Total score	0.82	0.90	0.59	0.54	0-72	2.7-5.6	4.7	4.0
DRS-P	0.66	0.85	0.56	0.48	0-36	1.2-2.8	2.4	2.8
DRS-E	0.68	0.76	0.42	0.32	0-8	0.5-0.7	1.0	1.1
F/WB	0.82	0.67	0.35	0.39	0-8	0.9-1.1	1.1	0.9

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Association of response to first-line chemotherapy with the efficacy of atezolizumab in patients with metastatic urothelial carcinoma.

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Background: In the current study, we evaluated whether the response first-line chemotherapy could impact atezolizumab benefit in terms of response rate and overall survival in patients with metastatic urothelial carcinoma. **Methods:** In this study, we present the retrospective analysis of 105 patients with urothelial cancer treated with ATZ after progression on first-line chemotherapy. The association between response to first-line chemotherapy and ATZ was assessed using Fisher's exact test. Overall survival (OS) was estimated by using the Kaplan-Meier method. Univariate analysis was used to identify clinical and laboratory factors that significantly impact OS. Variables were retained for multivariate analysis if they had a statistical relationship with OS ($p<0.1$) and then included the final model if $p<0.05$. **Results:** Best response to first-line chemotherapy was complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) in 5(4.8%), 38(36.2%), 16(15.2%), 46(43.8%) patients, respectively. Best response to atezolizumab was CR, PR, SD, PD in 9(8.6%), 22(21%), 23(21,9%), 51(48,5%). Forty (74.1%) of patients who benefited from first-line chemotherapy also benefited from atezolizumab, while only 14 (25.9%) of patients with initial PD after first-line chemotherapy subsequently experienced clinical benefit with atezolizumab (Fisher's exact test, p=0.001). Patients with clinical benefit from first-line chemotherapy had a higher OS. The median OS of atezolizumab were 14.8 and 3.4 months for patients with clinical benefit and progressive disease in response to first-line chemotherapy, respectively (log-rank p=0.001). In univariate analysis, Patients with clinical benefit from first-line chemotherapy, liver metastases, baseline creatinine clearance less (GFR)than 60 ml/min, Eastern Cooperative Oncology Group (ECOG) performance status ($1 \geq$), and hemoglobin levels below 10 mg/dl were all significantly associated with OS. Three of the adverse prognostic factors according to the Bellmunt criteria were independent factor of short survival: liver metastases (Hazard Ratio [HR]= 0.6; 95% CI 0.174-0.60; p=0.04), ECOG PS$\geq$1 (HR= 0.36; 95% CI 0.2-0.66; p=0.001), and Hemoglobin level below 10 mg/dl (HR= 0.36; 95% CI 0.2-0.66; $p < 0.001$). In addition, Patients with clinical benefit from first-line chemotherapy (HR= 0.39; 95% CI 0.24-0.65; $p < 0.001$) maintained a significant association with OS in multivariate analysis. **Conclusions:** Our study demonstrated that clinical benefit from first-line chemotherapy was independent prognostic factor on OS in patients' use of atezolizumab as second-line treatment in metastatic bladder cancer. Furthermore, these findings are important for stratification factors for future immunotherapy study design in patients with bladder cancer who have progressed after first-line chemotherapy. Research Sponsor: None.

A retrospective real-world major bleeding (MB) comparison of direct oral anticoagulants (DOAC) and low molecular weight heparin (LMWH) in genitourinary cancer-associated venous thromboembolism (GU-CAVTE) with reported randomized clinical trials (RTC).

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Background: MB is a serious complication in patients with CAVTE receiving treatment with DOAC or LMWH. The most recent meta-analysis of the four major RCT showed that MB events rate were similar among the DOAC and LMWH group, however, it was noted that MB occurred at GU site 4.9 times more in DOAC than LMWH patients. While GUCA (e.g. bladder and testicular) are considered to be high-risk based on the Khorana Score, they were underrepresented among the RCT ($<$ 12%). We present a Real-World retrospective cohort study analyzing the MB rates in patients presenting with GU-CAVTE treated either by a DOAC or LMWH compared to those of the RTC. **Methods:** We performed a retrospective chart review of patients with a diagnosed GUCA and VTE who presented to The University of Arizona Cancer Center (UACC) and were subsequently placed on anticoagulant therapy with either a DOAC or LMWH from 11/2013-4/2020. MB outcome was defined as documented Hgb drop of $\geq$2 g/dL, $\geq$2 units of PRBC, MB in a critical site, or contributing to death. MB was extracted and compared from the SELECT D, ADAM VTE, and Caravaggio for DOAC and Hokusai for the LMWH control arm with the GUCA subgroup. Recurrent VTE was collected. In situations where there was insufficient data to categorize individuals, those individuals were excluded from the analysis. The proportion of MB reported in each study were compared using a binomial test. **Results:** Our review included 56 patients with similar baseline characteristics to the RCT, who were prescribed enoxaparin (n = 13), apixaban (n = 27) and rivaroxaban (n = 16). Our UACC data was compared to the RCT reported MB outcomes with rivaroxaban (12% vs 8%, [p = 0.63]), apixaban (11% vs 6%, [p = 0.40]), and LMWH (both 0 vs 1% [p = 0.67]). No statistical difference among DOAC selection [p = 0.90]. Our UACC rate of MB in patients with GUCA for both DOAC combined versus LWMH were 11.6% (5/43) and 0% [p = 0.1910], compared to the RCT GU subgroup was 5.7% (6/104) [p = 0.02] and 0.6% (1/175) [p = 1.0], respectively. Furthermore, our data found no statistical significance difference among the recurrent VTE rate among DOAC, LMWH, UACC Retrospective or RCT events. **Conclusions:** In agreement with the four major RCT, our study demonstrated that patients with high-risk GUCA and underlying VTE treated with a DOAC had a non-significant higher incidence of MB compared to those treated with LMWH. Further, our Real-World experience showed that GUCA DOAC had a significantly higher MB event rate compared to the RCT subgroup population. We acknowledge there are inherent biases in all retrospective studies and RCT. These data support the idea that DOAC should be further studied and used with caution in patients with a high risk of bleeding. We recommend LMWH being the safest anticoagulation modality for High-Risk Bleeding GU malignancy. Research Sponsor: None.

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Safety and efficacy outcomes in immune checkpoint inhibitor (ICI)-treated metastatic urothelial carcinoma (mUC) patients (pts) requiring treatment interruption (TI) due to immune-related adverse events (irAEs).

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Background: Most patients (pts) with metastatic urothelial carcinoma (mUC) will receive immune checkpoint inhibitors (ICI) at some point during treatment. As such, understanding of immune-mediated toxicity is integral to optimal patient management. We describe the clinical characteristics, treatment, and outcomes of ICI-treated mUC pts who experienced irAEs requiring treatment interruption (TI). **Methods:** ICI-treated mUC pts who developed > grade 2 (per CTCAEv5) irAEs leading to >2 week TI were retrospectively reviewed. Patient-, disease-, treatment-, and toxicity-related data were evaluated. Toxicity was graded per CTCAEv5. Time to treatment interruption (TTI), treatment-free interval (TFI), time to next treatment (TTNT), and duration of response (DoR) were assessed descriptively. **Results:** Of 200 ICI-treated mUC pts, 18 (9%) experienced irAEs necessitating TI. 12 (43%) were male; median age at diagnosis was 72.5 (range, 45-80); 15 (83%) had KPS > 80. 8 (44%) had pure UC histology, 14 (78%) had prior cystectomy or nephroureterectomy, and 11 (61%) received platinum-based chemotherapy in the perioperative setting. 4 (22%) received 1L platinum-based Tx for mUC. ICI therapy was distributed evenly between atezolizumab (50%, n = 9) and pembrolizumab (50%, n = 9). Median TTI was 6.5 months (mos) (range, 1-19). The most common irAEs were dermatitis (22%, n = 4), colitis (17%, n = 3), and transaminitis (17%, n = 3); the majority were grade 2 (72%, n = 13). No grade 4/5 events occurred. 14 pts (78%) were treated with methylprednisolone and/or prednisone. Median initial prednisone-equivalent steroid dose was 45 mg/day (range, 30-1,250) with a median steroid duration of 42 days (range, 4-198). ICI were held and later re-challenged in 10 pts (56%), permanently discontinued in 7 pts (39%), and transitioned to a subsequent Tx in 1 pt (5%). Of 10 pts re-challenged with ICI, 7 (70%) experienced an irAE upon re-challenge (4 with recurrent irAEs, 3 with new irAEs); ICI was permanently discontinued in 3 of these pts. For pts receiving subsequent Tx, median TFI was 1 month (range, 0-12) and median TTNT was 5 mos (range, 2-31). Median DoR among all pts with initial response to ICI therapy was 15.5 mos (range, 2-52). Of 7 pts who permanently discontinued ICI and received no further Tx, 6 (86%) demonstrated an ongoing sustained therapy response with median DoR of 22.5 mos (range, 12-52). **Conclusions:** In this cohort, ICI-treated mUC pts who developed irAEs requiring treatment interruption had a high rate of subsequent irAEs upon ICI re-challenge. Importantly, pts who discontinue ICI due to irAE can have durable responses off treatment, consistent with data from other cancers.
Research Sponsor: None.

Trends over time in survival in patients with urothelial carcinoma in the real-world: A multicenter analysis.

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Background: Patients with muscle-invasive bladder cancer (MIBC) historically have poor long-term outcomes, with nearly 50% developing metastatic disease. Similarly, patients with metastatic urothelial carcinoma (mUC) have had median overall survivals of less than 2 years. Novel therapies have been implemented over time in attempts to improve outcomes. This study evaluates trends in survival over time in patients with MIBC and mUC treated in the real-world setting. **Methods:** Retrospective data was collected from two major cancer centres in Alberta and the Princess Margaret Cancer Centre in Ontario, Canada. Consecutive patients treated with platinum-based chemotherapy between 01/2005 and 01/2018 who had confirmed MIBC or mUC were evaluated. Patients were excluded if they had been treated as part of a clinical trial in the first-line setting. Patients were categorized based on year of diagnosis at presentation: time period 1 (T1) diagnosed between 01/2005 and 12/2011, and time period 2 (T2) diagnosed between 01/2012 and 12/2018. The co-primary endpoints were disease-free survival (DFS) for MIBC, progression-free survival (PFS) for mUC, and overall survival (OS) for both. **Results:** 572 patients were included, 196 (78% male; median age 63.8 years) had MIBC and 376 (76% male; median age 68.4 years) were treated for mUC. Amongst patients with MIBC, 33% (65) were treated in T1 and 67% (131) in T2. Median DFS and OS were significantly improved in T2 compared to T1 for patients with MIBC (Table). On multivariate analysis, earlier year of diagnosis and ECOG status $\geq$2 was independently associated with poor outcomes (p=0.016 and p=0.008, respectively). Amongst patients with mUC, 205 (55%) were treated in T1 and 171 (45%) in T2. Median PFS and OS did not significantly improve over time in patients with mUC from T1 to T2 (Table). **Conclusions:** In this real-world analysis, outcomes for patients with MIBC have significantly improved over time. This is likely attributed to standardization of perioperative chemotherapy protocols and improvements in surgical techniques. Similar improvements have not yet been demonstrated for patients with mUC during the two time periods. However, novel therapies (eg. immunotherapy) were only approved in 2017. Future analysis may explore the reasons for improvement in patients with MIBC and will evaluate outcomes in mUC patients treated from 2017 onwards. CI= confidence interval, HR= hazard ratio. Research Sponsor: None.

Median survival on multivariate analysis over time in patients with MIBC and mUC.

	Time Period 1 (2005-2011)	Time Period 2 (2012-2018)	
MIBC	**n=65**	**n=131**	
DFS, *months* (95% CI)	21.0 (13.5-28.4)	38.9 (8.5-69.3)	HR 0.58 (0.38-0.90) p=0.016
OS, *months* (95% CI)	33.8 (24.1-43.4)	82.8 (51.1-114.5)	HR 0.47 (0.30-0.74) p= 0.001
mUC	**n=205**	**n=171**	
PFS, *months* (95% CI)	5.1 (4.2-6.1)	6.2 (4.7-7.7)	HR 1.14 (0.92-1.41) p=0.225
OS, *months* (95% CI)	9.4 (8.2-10.6)	10.5 (8.2-12.8)	HR 1.14 (0.91-1.44) p=0.253

Association of survival and local radiotherapy to the bladder versus chemotherapy alone for patients with metastatic urothelial carcinoma (mUC).

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Background: Limited data exists on the role of local therapy for metastatic urothelial carcinoma of the bladder (mUC). Large database analysis have inherent limitations but can shed light on survival outcomes in a real-world population and in scenarios not easily studied in a randomized fashion. We hypothesized that in the NCDB, radiotherapy (RT) to the bladder plus chemotherapy (CT) would be associated with improved overall survival (OS) vs CT alone. **Methods:** We queried the NCDB for newly diagnosed mUC cases (cT1-4 N0-3 M1) from 2004-2015 treated with CT alone vs CT plus RT to $\geq$ 45 Gy to the bladder. Cystectomy patients were excluded. To account for lead time bias, we excluded patients with $<$ 2 months of follow-up. Variables for multivariable analysis (MVA) and matching included: age, sex, Charlson-Deyo comorbidity index (CCI), cT/N stage, facility type/location, insurance, year of diagnosis, and number of CT agents. Overall survival (OS) was estimated using the Kaplan-Meier method. Multivariable Cox proportional hazards analyses was performed. Propensity score matching (all variables) and exact matching (CCI score, age +/- 5 years, cT stage) was performed. **Results:** 4,459 patients with newly diagnosed mUC received either CT+ RT (n = 337) or CT alone (n = 4,122). Median follow-up was 10.7 months (range 2-144). Median RT dose was 57.6 Gy (IQR, 50.0– 63.0 Gy). Median OS for CT+RT was 13.8 (95% CI, 12.1-15.5) vs. 8.4 months (95% CI, 7.5-9.4) for CT ($P < 0.0001$). In MVA, RT was associated with improved OS (HR, 0.70; 95% CI, 0.62-0.79; $P < 0.0001$). Increasing age, comorbidity score, and cT-stage were associated with worse OS ($P < 0.001$). In subgroup analysis of patients without other comorbidities (CCI of 0), median OS for CT+RT was 14.4 (95% CI, 12.1-16.7) vs 11.1 months (95% CI, 10.7-11.5) for CT ($P = 0.001$). For patients with cT2-3N0 disease, median OS for CT+RT was 14.0 months (95% CI, 6.8-21.3) vs 10.9 months (95% CI, 10.1-11.7) for CT ($P = 0.001$). On propensity matched analysis (337 CT+RT and 337 CT patients), CT+RT was associated with improved OS (median 13.8 vs 8.5 months; $P < 0.0001$; MVA HR 0.59, 95% CI 0.50-0.69, $P < 0.0001$). On exact matched analysis (205 CT+RT and 205 CT patients), CT+RT was associated with improved OS (median 13.5 vs 9.9 months; $P = 0.002$; MVA HR 0.67, 95% CI 0.57-0.79, $P = 0.002$). Landmark analysis for patients living $\geq$6 months (median OS 16.3 vs 13.6 months, $P = 0.004$) and $\geq$12 months (median OS 22.2 vs 19.1 months, $P = 0.029$) demonstrated improved OS for CT+RT. **Conclusions:** In this large contemporary series, mUC patients treated with local RT plus CT had improved OS compared to CT alone. The magnitude of the effect persisted with matching and landmark analysis to try to mitigate the effect of selection bias, though we could not control for extent of metastatic disease. These findings are hypothesis-generating; a prospective trial evaluating the impact of bladder RT in mUC is warranted. Research Sponsor: None.

Treatment patterns among patients with advanced urothelial carcinoma following discontinuation of PD1/L1 inhibitor therapy.

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Background: There are a lack of published real-world data on treatment patterns for patients with locally advanced or metastatic urothelial carcinoma (la/mUC) previously treated with programmed death 1/ligand 1 inhibitor (PD-1/L1i) therapy. The objective of this study was to characterize the clinical characteristics and treatments among patients with la/mUC following discontinuation of first-line (1L) or second-line (2L) PD-1/L1i therapy. **Methods:** We performed a retrospective chart review at 26 geographically diverse clinical sites in the US. Patients aged ≥18 years with histologically or cytologically confirmed urothelial carcinoma and radiographic evidence of metastatic or locally advanced disease were identified. Included patients had initiated and subsequently discontinued PD-1/L1i therapy in the 1L or 2L setting for la/mUC between May 15, 2016-July 31, 2018. All patients had follow-up through October 31, 2019. Data were summarized using descriptive statistics. **Results:** Among the 300 patients included in the chart review, 198 (66%) received PD-1/L1i therapy as 1L and 102 (34%) as 2L therapy. Mean (SD) age at la/mUC diagnosis was 69.4 (8.7) years, and a majority of patients were male (66.0%) and White (74.7%). Consistent with age, most patients (82.7%) had comorbidities at la/mUC diagnosis; 39.7% hypertension, 23.7% coronary artery disease, 17.7% pulmonary disease, and 9.3% renal disease. At initiation of therapy, a higher proportion of patients who received 1L PD-1/L1i therapy had an Eastern Cooperative Oncology Group performance status of 2 or more than patients who received 2L PD-1/L1i therapy (36.8% vs 22.5%, respectively). Following discontinuation of PD-1/L1i therapy, 34% (n = 68) received subsequent therapy in 2L and 29% (n = 30) in third-line (3L). The most common subsequent therapies in 2L were gemcitabine monotherapy (24%), gemcitabine plus cisplatin or carboplatin (22%), PD-1/L1i therapy (22%), and taxane monotherapy (19%). The most common subsequent therapies received in 3L were taxane monotherapy (50%), pemetrexed (17%), and PD-1/L1i therapy (16%). Overall, switching from one PD-1/L1i therapy to another distinct PD-1/L1i therapy occurred in approximately 20% of patients, with "better efficacy/survival" noted by treatment teams as the most common reason for switching therapy among this subgroup. **Conclusions:** In this real-world case series, only a minority of patients with la/mUC who discontinued PD-1/L1i therapy received subsequent therapy. Among those that did, no clear standard of care was observed and approximately one-fifth of patients were treated with a second PD-1/L1i therapy after the first failed to control disease. Collectively, the data highlight significant unmet need for patients with la/mUC who discontinue PD-1/L1i therapy. Research Sponsor: Seattle Genetics and Astellas.

The prognostic impact of bone metastasis in urothelial carcinoma treated with first-line platinum-based chemotherapy.

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Background: Metastatic urothelial carcinoma (mUC) is an aggressive disease with a median overall survival (OS) of ≈ 15 months. In the first-line setting, key prognostic factors include ECOG performance status, white blood cell count, and response to treatment per the Galsky nomogram. Bone metastases (BM) in mUC are associated with morbidity and mortality but are grouped with visceral disease; hence, their impact on prognosis is not well established. We aimed to assess the survival impact of BM in mUC patients treated with first-line platinum-based chemotherapy (PBC). **Methods:** A retrospective collection of patient and tumor characteristics, with clinical response to treatment (complete response [CR], partial response [PR]; stable disease [SD] or progressive disease [PD]) for patients treated at Princess Margaret Cancer Centre, Tom Baker Cancer Centre, and Cross Cancer Institute from 2005-2018 was performed. Progression-free survival (PFS) and OS were estimated using the Kaplan-Meier method. Univariate (UVA) followed by multivariate analysis (MVA) of patient variables [Cox] using PFS and OS was performed. **Results:** Overall 376 mUC patients were included; 222 (59%) had soft-tissue metastases (STM) only, 70 (19%) had bone-only metastases, and 84 (22%) had both STM and BM. Overall, 35% had PR or CR, 19% had SD, and 39% had PD (7%: unknown response). The median PFS and OS for the whole cohort were 5.6 months (95%CI: 4.8-6.4) and 9.7 months (95% CI: 8.8-10.8) respectively. Select UVA by metastatic site showed inferior PFS for bone-only (p=0.03) and combination STM and BM (p=0.017). Only combination STM and BM were significant on UVA for OS (p=0.002). MVA showed that bone-only metastases (p=0.03) and ECOG 3-4 ($p<0.0001$) were associated with worse PFS (Table). Predictors of worse OS were the combination of STM and BM (p=0.02), ECOG 3-4 (p=0.001), and WBCs ≥ULN (p=0.02), (Table). **Conclusions:** BM are a significant predictor of worse outcomes for mUC patients treated with first-line PBC. Consideration as a treatment stratification factor for future studies is suggested. Strategies for the treatment of mUC patients with BM (ie: bone targeted agents) in the first-line setting should be addressed in future trials. Research Sponsor: None.

Predictors of outcomes in mUC (MVA).

	PFS		OS	
Variant	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Soft tissue only metastasis	REF	REF	REF	REF
Bone-only metastasis	**1.37 (1.04-1.82)**	**0.03**	1.22 (0.90-1.65)	0.19
Bone and soft tissue Metastasis	1.09 (0.84-1.42)	0.52	**1.40 (1.06-1.83)**	**0.02**
ECOG	REF	REF	REF	REF
0-2	**1.88 (1.41-2.51)**	**<0.0001**	**1.61 (1.21-2.15)**	**0.001**
3-4				
WBC's following 1st PBC	REF	REF	REF	REF
<11.000	1.04 (0.81-1.33)	0.74	**1.35 (1.05-1.74)**	**0.02**
≥11.000				
Response	REF	REF	REF	REF
(PD)	**0.19 (0.14-0.26)**	**<0.0001**	**0.34 (0.25-0.47)**	**<0.0001**
(SD)	**0.22 (0.17-0.29)**	**<0.0001**	**0.37 (0.29-0.48)**	**<0.0001**
(PR)	**0.09 (0.05-0.15)**	**<0.0001**	**0.14 (0.08-0.25)**	**<0.0001**
(CR)				

Urethral recurrence following radical cystectomy: Risk factors and outcomes.

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Background: Urethral recurrence (UR) has been reported to occur in up to 5% of patients following radical cystectomy (RC). Debate continues regarding the utility of screening for UR after RC. Moreover, oncologic outcomes of patients with UR remain incompletely described, and reports have been limited by small cohort sizes. Herein, we evaluated risk factors for UR as well as cancer-specific survival (CSS) and overall survival (OS) among patients with UR. **Methods:** We reviewed our institutional RC registry to identify patients with UR following RC. Logistic regression was used to assess risk factors for UR. Kaplan-Meier and Cox proportional hazard regression were used to compare outcomes in those with UR diagnosis prompted by symptoms versus those with asymptomatic UR diagnosed on surveillance cytology. **Results:** Overall, 2930 patients underwent RC from 1980-2018, with a median post-operative follow-up of 4.9 years (IQR 1.6-11.0), of whom 144 (4.9%) were subsequently diagnosed with UR. Prostatic urethral involvement at RC (odds ratio [OR] 5.75 [3.67-9.01], $p < 0.0001$) and higher pT-stage (OR 3.57 [2.07-6.14], $p < 0.0001$) were associated with an increased risk of UR, whereas receipt of continent urinary diversion (OR 0.34 [0.20-0.58], $p < 0.0001$) was associated with a decreased risk of UR. A total of 72/144 (50%) patients were diagnosed with UR based on symptoms, and 104/144 (72.2%) patients with UR underwent subsequent urethrectomy. Patients with symptomatic recurrence had higher tumor stage on urethrectomy than those with asymptomatic recurrence (≥pT2 in 13.1% vs 3.1%, $p = 0.007$). At a median follow-up of 2.6 years (IQR 1.0-7.1) after UR, 68 of the patients with UR died of urothelial carcinoma. Kaplan-Meier analyses suggest longer median overall and cancer-specific survival for patients with UR detected by cytology than those presenting with symptoms ($p = 0.05$ for both). On multivariable analyses, patients who experienced UR had significantly increased risk of cancer-specific (hazard ratio [HR] 1.93 [95% confidence interval 1.50-2.50], $p < 0.0001$) and all-cause mortality (HR 1.34 [1.13-1.65], $p = 0.001$). **Conclusions:** Approximately 5% of patient undergoing RC experience UR, with higher pT-stage and prostatic urethral involvement increasing the risk of UR. Asymptomatic detection of UR was associated with lower pathologic stage at urethrectomy as well as longer cancer-specific and overall survival, supporting urethral surveillance after RC. Research Sponsor: None.

The effect of antibiotic use within 30 days of initiation of immune checkpoint inhibitor (ICI) efficacy in patients with metastatic urothelial carcinoma (mUC) in real-world setting.

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Background: There is emerging evidence that patients (pts) treated with immune-checkpoint inhibitors (ICIs) may have a poorer response in the setting of antibiotic use (ABx), possibly due to negative impact on gut microbiota. Our group previously demonstrated that Abx use 60 days before or 60 days in mUC pts after initiation of ICI therapy did not have a significant impact on overall survival (OS) in real-world setting. We now studied the effect of Abx use within 30 days of initiation of ICI on OS in the same cohort of mUC patients. **Methods:** We performed a retrospective analysis of adult pts with mUC treated at the Cleveland Clinic between 2015 and 2020. Pts included in the study received at least 2 cycles of ICI therapy with either atezolizumab or pembrolizumab. Statistical analysis included study of OS in weeks using the Kaplan Meier method and rank log test, Fischer's exact test, and Kruskal-Wallis test. **Results:** A total of 115 pts that received ICI therapy were included. 57 pts received atezolizumab and 58 pts received pembrolizumab. 38 pts (33%) received antibiotics and 77pts (67%) did not. The most commonly used Abx used were Cephalosporins (27%), Penicillins/Carbapenems (25%), Flouroquinolones (23%), and Bactrim (11%). 18 pts received Abx within 30 days before initiation of ICI, 13 pts received Abx within 30 days after initiation of ICI, and 7 pts received Abx before and after initiation of ICI. There was no statistical difference in OS in the group of pts that received Abx 30 days prior to initiation of ICI with median OS of 5.95 months (95% CI 3.22-13.67, p=0.0695) compared to 12.39 months (95% CI 10.09 – 18.6) in those who did not receive Abx. Similarly, there was no statistical difference in OS in the group of pts that received Abx 30 days after initiation of ICI with median OS of 5.09 months (95% CI 2.53-22.57, p=0.2339) compared to 12.02 months (95% CI 8.6`-17.02 Table). **Conclusions:** In our single institution study of mUC patients receiving ICI treatment, the use of Abx did not affect the OS. Although there was a trend for better OS seen in pts who did not receive Abx, it was not statistically significant (Table). Due to the limitations of a retrospective analysis and small sample size, further studies are warranted taking into account other factors that may affect gut microbiota in mUC pts. Research Sponsor: None.

Antibiotic use, timing and effect on OS in mUC patients on ICI.

Antibiotics use before and after initiation of ICI		N	OS (months)	95% CI (months)	p-value
30 days before ICI initiation	No Abx 30 days before ICI	90	12.39	10.09-18.6	0.0695
	Abx use 30 days before ICI	25	5.95	3.22-13.67	
30 days after ICI initiation	No Abx 30 days after ICI	95	12.02	8.6-17.02	0.2339
	Abx use 30 days after ICI	20	5.09	2.53-22.57	

Germline alterations in cancer susceptibility genes in women with high-risk bladder cancer: Implications for germline testing and clinical management.

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Background: Gender differences exist in bladder cancer incidence, stage at diagnosis, and outcomes. Women have lower incidence of bladder cancer but are diagnosed with more advanced disease at presentation. They also have less favorable outcomes even after adjusting for tumor stage and treatment modality. The biologic mechanisms underlying gender disparities in bladder cancer remain unknown. **Methods:** We leveraged a prospective matched tumor-normal genomic profiling initiative to determine the prevalence and spectrum of pathogenic/likely pathogenic (P/LP) germline variants in women with bladder cancer. Germline DNA was tested for mutations in ≥77 cancer susceptibility genes using next-generation sequencing in 686 patients with bladder cancer. Mutation frequency and clinical characteristics were assessed by gender. **Results:** A total of 184 (27%) women and 502 (73%) men with bladder cancer underwent germline testing; median age of diagnosis was 66 ± 11.3 and 65 ± 11.3 years, respectively. Twenty-two women (12%) had bladder cancer diagnosis at age ≤ 50 years. Both groups had similar rate of tobacco exposure (57% vs 63%, p = 0.1), family history of bladder cancer (10% vs 10%, p = 0.5), and disease stage at diagnosis (non-muscle invasive bladder cancer [NMIBC] 54% vs 54%, MIBC 38% vs 39%, and metastatic disease 8% vs 6%, p = 0.7). Women had more non-urothelial carcinoma histology than men (adenocarcinoma 5% vs. 1%; squamous cell carcinoma 1% vs 0.2%, p = 0.001). More P/LP germline variants were found in women than men (38 [21%] vs. 70 [14%], p = 0.04). Twenty-eight women (15%) had P/LP variants in DNA-damage repair (DDR) genes; 23 (13%) carried moderate/high penetrance germline mutations, the most common were *BRCA1/2*, *CHEK2*, *NBN*, *ATM*, and *MITF*. Current clinical guideline for referral for genetic testing failed to identify 12 (52%) women with moderate/high penetrance germline mutations. Nine women (5%) carried germline mutations associated with increased risk of ovarian/endometrial cancers (*BRCA1/2* [5], *ATM* [2], *MLH1* [1], *TP53* [1]). **Conclusions:** Deleterious germline alterations are commonly present in women with high-risk bladder cancer. The presence of germline variants in some genes, such as BRCA1/2, can guide cancer screening and risk-reducing surgeries for patients and their families. Women with high-risk bladder cancer should be evaluated for suitability of germline testing, especially those who desire preservation of uterus and ovaries at the time of radical cystectomy, to rule out the presence of P/LP variants that increase risk of future gynecologic malignancies. Research Sponsor: U.S. National Institutes of Health.

Cost-effectiveness analysis of neoadjuvant immune checkpoint inhibition (ICI) versus cisplatin-based chemotherapy (CBC) in muscle-invasive bladder cancer (MIBC).

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Background: Multiple single-arm clinical trials have shown promising pathologic complete response (pCR) rates with neoadjuvant ICIs in MIBC. However, ICIs remain costly. We conducted a cost-effectiveness analysis comparing neoadjuvant ICIs with CBC. **Methods:** We applied a decision analytic simulation model with a health care payer perspective and two-year time horizon to compare neoadjuvant ICIs vs CBC. For the primary analysis we compared pembrolizumab with dose dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC). We performed a secondary analysis with gemcitabine/cisplatin (GC) as CBC and exploratory analyses with atezolizumab or nivolumab/ipilimumab as ICIs (vs both ddMVAC and GC). We input pCR rates from trials (ICIs) or a weighted average of prior studies (CBC) and costs from average sales price. Outcomes of interest included costs, 2-year recurrence-free survival (RFS), and incremental cost-effectiveness ratio (ICER) of cost per 2-year RFS. A threshold analysis estimated a pCR rate or price reduction for ICI to be cost-effective and one-way and probabilistic sensitivity analyses were performed. **Results:** Results of the cost effectiveness analysis are shown in the table. The incremental cost of pembrolizumab compared with ddMVAC was $8,042 resulting in an incremental improvement of 0.66% in 2-year RFS for an ICER of $1,218,485 per 2-year RFS. A pCR of 71% or a 26% reduction in cost of pembrolizumab would render it more cost-effective with an ICER of $100,000 per 2-year RFS. GC required a 96% pembrolizumab cost reduction to achieve an ICER of $100,000 per 2-year RFS. Atezolizumab appeared to be more cost-effective than ddMVAC, even though the 2yr RFS was 0.66% worse. **Conclusions:** ICIs were not cost-effective as neoadjuvant therapies, except when atezolizumab was compared with ddMVAC. Pembrolizumab would approach cost-effective thresholds with 26% or 96% reduction in cost when compared to ddMVAC and GC, respectively. Randomized clinical trials, larger sample sizes and longer follow-up are required to better understand the value of ICIs as neoadjuvant treatments. Research Sponsor: U.S. National Institutes of Health.

	Cost	Incremental Cost	2yr RFS	Incremental 2yr RFS	ICER (per 2yr RFS)
Chemotherapy (GC)	$529	Ref	0.5848	Ref	Ref
Pembrolizumab	$30,556	$30,027	0.5914	0.0066	$4,549,545
Atezolizumab	$18,838	$18,309	0.5782	-0.0066	DOMINATED
Nivolumab + Ipilimumab	$74,052	$73,523	0.6112	0.026	$2,784,962
Chemotherapy (ddMVAC)	$22,515	Ref	0.5848	Ref	Ref
Pembrolizumab	$30,556	$8,042	0.5914	0.007	$1,218,485
Atezolizumab	$18,838	-$3,677	0.5782	-0.0066	$557,121*
Nivolumab + Ipilimumab	$74,052	$51,537	0.6112	0.026	$1,952,159

*Saved with atezolizumab (vs ddMVAC).

Alignment and discordances in perceptions and experiences of shared decision making (SDM) among bladder cancer (BC) patients and their care team.

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Background: To align BC treatment with patient goals, it is vital that healthcare providers (HCPs) engage their patients (pts) in SDM for treatment planning. We assessed alignment and discordances on aspects of SDM among BC pts and their urology and oncology teams. **Methods:** Between 05/2020 and 06/2020, surveys were administered to 53 pts with BC (48% female, mean age 68 years) and 23 HCPs, as part of in-clinic and virtual collaborative patient education sessions across 5 US-based practices. Surveys were designed to assess perceptions, preferences, and experiences with regard to SDM during BC care. **Results:** Survey findings indicated key alignments and discordances in pts' reported experience and HCPs' perceptions of the use of SDM in BC care. HCPs and pts identified the same top 2 patient goals for BC care: 1) preventing progression/recurrence (61% pts, 48% HCPs) and 2) maintaining quality of life (35% pts, 78% HCPs). When asked to identify patient's top challenges for pts in BC care, both pts and HCPs indicated post-treatment aspects as the top challenge, though pts indicated managing side effects/serious worry about side effects from treatment as the top challenge (22%); whereas, HCPs were split evenly between managing side effects from treatment (26%) and managing life changes as a result of urinary diversion (26%). HCPs overestimated the effect that fatigue and worry had on pts capacity for SDM: only 9% of pts indicated worry or fatigue as a barrier to SDM, but 65% of HCPs indicated this as a likely barrier. Furthermore, the patient experience of SDM differed from HCP perception of SDM (Table); for some aspects of SDM, such as explaining different treatment options, explaining pros/cons of treatment options, and overall involvement in treatment decisions, fewer HCPs indicated that these aspects of SDM always or usually occurred as compared to pts. **Conclusions:** These findings reveal important alignments and discordances between pts and HCPs with regard to BC care and SDM, which may inform future bladder cancer and SDM initiatives. Research Sponsor: Educational Grant from Genentech.

Survey results.

Aspect of SDM Reported as Always or Usually Occurring	Patient Reported (%)	Physician Perceived (%)
Asks how BC affects patient daily activities/quality of life	44	52
Asks about patient BC treatment goals	31	43
HCP tells patient about different options for treating your BC	57	26
HCP explains pros/cons of each treatment choice	47	35
Care team works with patient to create a BC treatment plan to meet patient needs/goals	57	36
How involved are pts in decisions around their treatment options	56	43

421 **Poster Session**

Is there value to routine oncologic surveillance after radical cystectomy? Comparative outcomes of symptomatic versus asymptomatic recurrence.

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Background: Reported rates of adherence to post-radical cystectomy (RC) surveillance guidelines in real-world practice have been as low as 9%, in part reflecting a nihilistic view held by many of the value of routine follow-up. Indeed, conflicting data exist regarding the outcomes of patients with cancer recurrence detected by scheduled surveillance versus symptom-directed evaluation. Herein, we assessed comparative outcomes of patients with symptomatic recurrence (SR) versus asymptomatic recurrence (AR) after RC. **Methods:** We reviewed our Institutional Registry of RC patients to identify patients with cancer recurrence following RC. Presenting symptoms in the SR cohort included pain, constitutional symptoms, gastrointestinal symptoms, and hematuria/voiding symptoms, whereas AR was defined as recurrence detected on routine surveillance in the absence of symptoms. Baseline demographic and clinical characteristics were compared between study groups using chi-square and t-test. Kaplan-Meier and Cox survival analyses were performed to compare cancer-specific survival (CSS) and overall survival (OS) between AR and SR groups. **Results:** Of 3822 patients who underwent RC from 1980-2018 (with a median follow-up after RC of 2.4 years (IQR 1.1,5.5), a total of 1100 were subsequently diagnosed with recurrence, including 311 (28.3%) with AR and 789 (71.7%) with SR. Median time from RC to recurrence was longer in the AR group (13.2 months) than in the SR group (10.8 months; $p = 0.01$). Presenting symptoms included pain (70.2%), constitutional symptoms (50.7%), gastrointestinal symptoms (23.3%), and urinary symptoms (23.3%). Median follow-up after recurrence was 2.4 years (IQR 1.1-5.5), during which time 997 patients died, including 840 who died of bladder cancer. Compared to patients with SR, patients with AR had a longer median CSS (54.5 months vs 27.3 months, $p < 0.001$) and OS (43.0 months vs 25.8 months, $p < 0.001$). On multivariable Cox proportional hazards models adjusting for demographic and clinical factors, SR was associated with a significantly increased risk of cancer-specific (hazard ratio [HR] 1.66 [95% confidence interval 1.41-1.96], $p < 0.0001$) and all-cause mortality (HR 1.48 [1.23-1.71], $p < 0.0001$). **Conclusions:** SR after RC is associated with worse oncologic outcomes than post-RC recurrence detected by routine surveillance. As such, continued surveillance is warranted, while further study is needed to determine the optimal follow-up regimen balancing patient and disease risks. Research Sponsor: None.

Bladder cancer research funding in Canada and the United States: A comparison between stakeholder priorities and resource allocation from 2017 to 2019.

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Background: There is an increasing emphasis on patient-centered research to encourage cancer care that is responsive to patients' needs. Previously, the Bladder Cancer Advocacy Network (BCAN) Patient Survey Network (PSN) engaged patients and other key stakeholders and compiled a prioritized list of research questions in bladder cancer. However, it is uncertain whether these priorities have successfully guided subsequent resource allocation by funding agencies. The purpose of this study was to understand how bladder cancer research funding has been allocated in recent years and to determine whether funding patterns have aligned with patient and caregiver priorities. **Methods:** We investigated publicly available research databases online or contacted agencies directly to determine bladder cancer research fund allocation in Canada and the US from 2017 to 2019. Each funding competition and all funded projects were evaluated to assess whether they aligned with previously identified priority research areas. Trends in funding allocation were assessed and several key variables including country, year, agency focus, cancer stage, and funding amount were analyzed. **Results:** Fifteen agencies provided funding to bladder cancer research between 2017 and 2019, amounting to a total of $78,525,974 in funding for 298 projects across Canada and the US. Of this funding, $23,268,258 (30%) went towards projects addressing the stakeholder-identified high priority research questions, $15,575,064 (20%) went towards projects addressing lesser priority questions, and the remaining $39,682,652 (50%) funded projects addressing questions which did not align with previously identified stakeholder priorities. General agencies (non-bladder cancer-specific) funded more priority (high and lesser) projects than bladder cancer-specific agencies ($p < 0.001$). Among projects addressing non-muscle invasive bladder cancer, 36% of funding went to high priority areas, compared to 13% and 27% for muscle-invasive bladder cancer and metastatic bladder cancer, respectively. Among the top 10% of projects (n = 30) with the greatest funding amount (combined $43,249,792), 45% of the funding went to high priority areas, 21% went to lesser priority areas, and 34% went to non-priority areas. **Conclusions:** Of nearly $80,000,000 USD allocated to bladder cancer research in recent years, approximately half was allocated to projects addressing stakeholder-identified priority areas while half was allocated to projects that were not aligned with stakeholder priorities. More work is needed to ensure stronger alignment between stakeholder-identified priority areas and funding allocation in bladder cancer research. Research Sponsor: None.

The association of malnutrition and sarcopenia with geriatric assessment impairment and outcomes in patients with bladder cancer undergoing cystectomy.

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Background: Malnutrition and sarcopenia are linked to decreased functional status in older adults with malignancy, but their effect on geriatric assessment (GA) impairment in patients with bladder cancer (BC) undergoing radical cystectomy (RC) is unknown. We investigated the association between malnutrition and sarcopenia with GA impairment and postoperative outcomes. **Methods:** Patients with BC undergoing RC between 2012 – 2019 were enrolled in a prospective cohort study of GA before RC. Malnutrition was evaluated by a dietitian pre-RC per the Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition diagnostic criteria. Sarcopenia, defined by a skeletal muscle index of < 52.4 cm^2/m^2 in males and < 38.5 cm^2/m^2 in females, was determined using SliceOmatic software to analyze pre-RC CT images at the L3 vertebra. Patients with vs without malnutrition and those with vs without sarcopenia were compared using Fisher's exact and Wilcoxon rank sum tests. **Results:** Of 73 patients, 59 had GA + nutrition evaluation and 51 had GA + sarcopenia assessment (overall median age 68 [IQR 62-74], 76% male). The prevalence of malnutrition was 7% and sarcopenia was 63%. A numerically greater proportion of patients with malnutrition or sarcopenia were impaired on ≥ 1 GA measure compared to those without malnutrition (100% vs 78%, p=0.57) or sarcopenia (78% vs 68%, p=0.52), although this was not statistically significant (Table). Median hospital length of stay (LOS) was increased for patients with vs without sarcopenia (4 vs 5 days, p=0.005). Post-RC complication rate was similar for patients with vs without malnutrition (100% vs 75%, p=0.56) and patients with vs without sarcopenia (81% vs 74%, p=0.73), but malnourished patients were more likely to have Clavien-Dindo grade 3+ complications than those without malnutrition (100% vs 27%, p = 0.009). **Conclusions:** In our cohort of patients with BC undergoing RC, those with malnutrition or sarcopenia may have an increased rate of impairment on GA compared to those without malnutrition or sarcopenia. Sarcopenia was associated with increased LOS while malnutrition was associated with increased major complications. Our results are limited by small sample size, and future work is needed to elucidate whether addressing these modifiable factors improves functional status and postoperative outcomes. Research Sponsor: U.S. National Institutes of Health.

	No malnutrition (n=55)	Malnutrition (n=4)	p	No sarcopenia (n=19)	Sarcopenia (n=32)	p
Age, years*	66 (61-74)	68.5 (68-71.5)	0.48	62 (57-72)	72 (62.5-77)	0.04
≥ 1 GA impairment (%)	43 (78)	4 (100)	0.57	13 (68)	25 (78)	0.52
Median % of GA measures impaired on	12.5	27.2	0.25	11.1	8.7	0.62
RC LOS, days*	5 (4-6)	7 (4-31)	0.42	4 (4-5)	5 (4-6)	0.005
Any post-op complication	41 (75)	4 (100)	0.56	14 (74)	26 (81)	0.73
Grade 3+ post-op complication	15 (27)	4 (100)	0.009	5 (26)	8 (25)	1

*Median (IQR).

Patient, caregiver, and provider reported risk-benefit acceptance thresholds in non-muscle invasive bladder cancer (NMIBC) trial designs.

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Background: FDA guidelines for NMIBC clinical trial design have stimulated a marked increase in NMIBC trial conduct. However, NMIBC patient (PT) input to define acceptable treatment toxicity thresholds and clinical measures most meaningful to NMIBC PTS has been lacking. We conducted a survey to investigate treatment side effect tolerance levels, respondent-ranked clinical relevance of various trial efficacy measures, and differences in responses between PTS, caregivers (CG), and healthcare providers. **Methods:** In 8/2018, an NMIBC Patient-Driven Endpoints working group was formed at the Bladder Cancer Advocacy Network (BCAN) Think Tank meeting. Through iterative focus groups, a 21-question survey composed of 4 domains (demographics, treatment history, acceptable toxicity thresholds, and clinical benefit metrics) was designed. The BCAN Patient Survey Network and other social media platforms were utilized to distribute and publicize the survey. A unique IP address was required to eliminate duplicate respondents. Categorical and ordinal variables were reported as frequencies with 95% confidence intervals. Continuous variables were reported as medians with ranges. Frequency differences in specific variables of interest according to respondent roles were assessed by Chi-square testing with significance set at $p < .05$. **Results:** From 7/18-8/30/20, 845 survey responses were recorded. Key demographics included: 647 (76.7%) PTS, 77 CG (9.1%), 67 urologists (UROL) (7.9%), 35 medical oncologists (ONC) (4.1%), 59.8% male, 85.0% Caucasian non-Hispanic, median age 64.0 years, and 62.7% with NMIBC at diagnosis. Any reversible toxicity was deemed acceptable in 68.8% of PT, 61.0% of CG, 62.7% of UROL, and 54.3% of ONC respondents $p = 0.09$. Any permanent toxicity was deemed acceptable by 15.6% of PT, 11.7% of CG, 16.4% of UROL, and 20.0% of ONC respondents $p = 0.54$. Differences in acceptance of individual treatment related toxicities according to roles were observed $p < .05$ and will be presented. Mean rank order of potential clinical trial endpoints with a rank of 1 for most clinically meaningful benefit to 5 for least meaningful were 1.96 for avoidance of cystectomy, 2.13 for prevention of muscle invasion, 2.87 for 24-month recurrence free survival (RFS), 3.55 for 12-month RFS, and 3.97 for complete response rate with little variation according to respondent roles. **Conclusions:** Threshold levels for global reversible and permanent treatment toxicity rates were similar across respondent roles. Complete response was consistently ranked lowest in clinical relevance among all respondent roles. These survey results provide important patient and provider benchmarks for acceptable toxicity thresholds within future NMIBC trial designs and suggest an increased emphasis on bladder preservation and durability of response in evaluating the merits of new NMIBC therapies. Research Sponsor: Bladder Cancer Advocacy Network.

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Avelumab (Ave) first-line (1L) maintenance plus best supportive care (BSC) versus BSC alone for advanced urothelial carcinoma (UC): JAVELIN Bladder 100 Japanese subgroup analysis.

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Background: A randomized phase III trial (JAVELIN Bladder 100; NCT02603432) to investigate avelumab (anti–PD-L1) as 1L maintenance therapy in patients with advanced UC met its primary objective, demonstrating significantly prolonged overall survival (OS) with Ave + BSC vs BSC alone in all randomized patients and in patients with PD-L1+ tumors. We report efficacy and safety in Japanese patients enrolled in this study. **Methods:** Eligible patients with unresectable locally advanced or metastatic UC that had not progressed with 4-6 cycles of gemcitabine with either cisplatin or carboplatin were randomized 1:1 to receive maintenance Ave (10 mg/kg IV every 2 weeks) + BSC or BSC alone, stratified by best response to 1L chemotherapy (complete/partial response vs stable disease) and by visceral vs nonvisceral disease when initiating 1L chemotherapy. The primary endpoint was OS, assessed from randomization in all randomized patients and in patients with PD-L1+ tumors (Ventana SP263 assay). Secondary endpoints included progression-free survival (PFS) per blinded independent central review and safety. **Results:** Japanese patients (n=73) were randomized to receive Ave + BSC (n=36) or BSC alone (n=37); 52.8% vs 62.2% had PD-L1+ tumors, respectively. Median OS (95% CI) was 24.7 months (18.2-not estimable [NE]) with Ave + BSC vs 18.7 months (12.8-33.0) with BSC alone (HR, 0.81 [95% CI; 0.409-1.585]) in all randomized patients and 18.6 months (9.4-NE) with Ave + BSC vs 19.4 months (11.7-33.0) with BSC alone (HR, 1.00 [95% CI, 0.413-2.412]) in patients with PD-L1+ tumors. Median PFS (95% CI) was 5.6 months (1.9-9.4) with Ave + BSC vs 1.9 months (1.9-3.8) with BSC alone (HR, 0.63 [95% CI, 0.358-1.113]) in all randomized patients and 5.6 months (1.8-11.2) with Ave + BSC vs 1.9 months (1.9-3.8) with BSC alone (HR, 0.62 [95% CI, 0.298-1.301]) in patients with PD-L1+ tumors. The most common treatment-emergent adverse events (all grade; grade $\geq$3) in the Ave + BSC arm were pyrexia (10 [27.8%]; 0), nasopharyngitis (7 [19.4%]; 0), and anemia (7 [19.4%]; 4 [11.1%]). **Conclusions:** Ave 1L maintenance + BSC was efficacious and tolerable in Japanese patients with advanced UC, and results were generally consistent with those in the overall population. Clinical trial information: NCT02603432. Research Sponsor: Pfizer, as part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.

Management of fibroblast growth factor receptor inhibitor (FGFRi) treatment-emergent adverse events (TEAEs) of interest in patients (Pts) with locally advanced or metastatic urothelial carcinoma (mUC).

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Background: Erdafitinib (ERDA), a pan-FGFR kinase inhibitor, was US FDA approved for adults with mUC with susceptible *FGFR3/2* alterations (*FGFRa*) who progressed on ≥ 1 line of prior platinum-based chemotherapy based on primary results of the BLC2001 trial (NCT02365597). At final analysis (median 2-y follow-up), ERDA showed median OS of 11.3 mo and a manageable safety profile. Some FGFRi toxicities are distinct from those of other small-molecule TKIs. Proactive AE management can avoid treatment discontinuation, ensuring maximum benefit. We report the frequency and management of TEAEs of interest (central serous retinopathy [CSR], hyperphosphatemia ["on-target" FGFRi class effect], stomatitis, and skin and nail toxicities) for the optimal schedule of ERDA from the final analysis of BLC2001. **Methods:** The open-label, phase II BLC2001 study enrolled pts with measurable mUC, prespecified *FGFRa*, and progression during/after ≥ 1 line of prior chemotherapy or ≤ 12 mos of (neo)adjuvant chemotherapy or who were cisplatin ineligible, chemo naive. Optimal dose schedule in the study was 8 mg/d continuous ERDA in 28-d cycles with uptitration to 9 mg/d (ERDA 8 mg/d UpT) if prespecified serum phosphate level was not reached and no significant TEAEs occurred. ERDA 8 mg/d UpT safety results as of Aug 9, 2019 (final analysis) are summarized here. AEs were graded using NCI CTCAE v4.0. **Results:** Median follow-up for 101 pts treated with ERDA 8 mg/d UpT was 24.0 mos; median treatment duration was 5.4 mos. All pts had ≥ 1 TEAE. Hyperphosphatemia, stomatitis, nail disorders, skin disorders, and CSR TEAEs occurred in 78%, 59%, 59%, 55%, and 27% of pts, respectively (few were grade [gr] 3; none were gr ≥ 4; Table). TEAEs were mostly managed with concomitant treatment and dose modifications. As of data cutoff, hyperphosphatemia had resolved in 74/79 (94%) pts; stomatitis in 44/60 (73%); nail and skin TEAEs in 26/60 (43%) and 25/55 (45%), respectively; and CSR in 17/27 (63%). Most unresolved TEAEs were gr 1–2. No treatment-related deaths occurred. **Conclusions:** ERDA had measurable benefit in pts with advanced UC with *FGFRa*. As with other targeted therapies, exposure to ERDA is associated with a pattern of AEs. The most common and FGFRi class effect TEAEs were generally reversible and managed by supportive care and dose modification. Clinical trial information: NCT02365597. Research Sponsor: Janssen Research & Development, LLC.

N = 101	Hyperphosphatemia	Stomatitis	Nail	Skin	CSR
Overall incidence, n (%)	79 (78)	60 (59)	60 (59)	55 (55)	27 (27)
Gr 1	54 (54)	21 (21)	22 (22)	25 (25)	12 (12)
Gr 2	23 (23)	25 (25)	23 (23)	22 (22)	11 (11)
Gr 3	2 (2)	14 (14)	15 (15)	8 (8)	4 (4)
Median time to onset, d	20	32	69	42	53
Led to dose reduction[a], n (%)	11 (11)	19 (19)	20 (20)	11 (11)	13 (13)
Led to dose interruption[a], n (%)	24 (24)	27 (27)	17 (17)	13 (13)	8 (8)
Treatment discontinued, n (%)	1 (1)	2 (2)	1 (1)	3 (3)	3 (3)

[a] TEAEs leading to dose interruption followed by reduction reported as reduction.

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Healthcare resource utilization (HCRU), costs, and mortality in relation to select immune-related adverse events (irAEs) and line of therapy (LOT) in patients (pts) with advanced or metastatic urothelial cancer (UC) treated with immune checkpoint inhibitor (ICI) monotherapy.

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Background: Data on HCRU and costs in US UC patients treated with ICIs is in its infancy, as there is little information by LOT or focused on irAEs due to ICI use. In addition, the relationship between irAEs and mortality is controversial, with some studies suggesting lower risk of mortality in pts with irAEs, whereas others have found no association between irAEs and mortality. We assessed the associations of 1) irAEs and 2) LOT with HCRU, costs, and mortality in UC pts treated with ICI monotherapy. **Methods:** This retrospective cohort study used administrative claims data linked with mortality data from the National Death Index and Social Security Death Index to identify US commercial and Medicare Advantage plan members with UC treated with ICI monotherapy between 1 Sep 2014 and 30 Apr 2019. The LOT number of ICI therapy was captured. Twenty-one irAEs were chosen a priori based on ASCO and NCCN guidelines and clinical input. Based on ICD codes from claims, newly occurring irAEs were captured from ICI initiation to the earliest of 6 months after initial ICI LOT ended, start of new treatment, death, disenrollment, or 30 Apr 2019; HCRU and costs were assessed during same time. Using Cox regression with ICI LOT and time-varying irAEs as the exposures, we computed adjusted hazard ratios (HRs). Lin's regression analysis was used to calculate adjusted 6-month all-cause costs by irAE. **Results:** Among UC pts treated with ICI monotherapy (N=417; mean age 74 $\pm$ 10 years; 72% male; 17% received prior systemic steroids; 32% initiated ICI as LOT 1, 43% as LOT 2), 22% (n=90) had an irAE. Pts who received ICIs as 2L therapy were 1.5 (95% CI: 1.1-2.0) and 1.7 (95% CI: 1.2-2.4) times more likely to have an all-cause ER visit and inpatient stay, respectively, than those who received 1L. There was no difference in mortality risk between 2L and 1L subgroups (HR, 1.2 [95% CI: 0.9-1.6]). Pts with irAEs had a 60% higher risk of an all-cause ER visit (95% CI: 1.0-2.5) and more than double the risk of an all-cause inpatient stay (HR, 2.6 [95% CI: 1.7-4.0]) than pts without irAEs. Pts who experienced an irAE had higher mean all-cause healthcare costs over 6 months vs those without irAEs ($98,415 vs $75,300; $p<0.001$). Mortality rates were similar between UC pts with and without irAEs (HR, 1.2 [95% CI: 0.9-1.6]). **Conclusions:** Pts with irAEs had higher all-cause HCRU and costs than pts without, and pts who received ICIs as 2L therapy had higher HCRU and costs than those who received 1L. This real-world study did not find that irAEs were associated with mortality in UC pts treated with ICI monotherapy. To inform optimum use of ICIs and management of irAEs, future work should include longer follow-up and grade of severity and number of irAEs. Research Sponsor: Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer.

INTACT (S/N1806) phase III randomized trial of concurrent chemoradiotherapy with or without atezolizumab in localized muscle-invasive bladder cancer: Safety update on first 73 patients.

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Background: Trimodality therapy (TMT) with maximal TURBT followed by chemoradiation(CRT) is a standard of care for select patients with muscle invasive bladder cancer (MIBC). This trial evaluates the activity of atezolizumab (atezo) in MIBC in combination with TMT. This trial was designed with pre-specified safety analyses of the first 80 patients (40 in each arm). At the time of SWOG fall 2020 DSMC report deadline we had enrolled 84 patients but data on only 73 patients were available. The same data are being submitted to ASCO GU meeting. **Methods:** This trial is testing atezo every 3 weeks for 6 months given concurrently and adjuvantly with CRT vs. CRT alone in 475 patients with MIBC T2-T4aN0M0 disease. Patients are stratified based on PS; T2 vs T3 or T4; choice of chemotherapy; and radiation field (bladder only vs small pelvis). Patients undergo biopsy 3 months after finishing CRT to assess treatment response. Patients are followed for 5 years for recurrence or survival. This trial was not preceded by a phase I study but was designed with a safety run in of 80 patients. Study team agreed on the study design based on available data from other tumor types and initial experience from investigators running smaller similar trials. It was pre-specified that if we observe more than 25% patients having grade 3-5 colitis or cystitis in the atezo arm or any other toxicity which is deemed clinically significant and related to atezo, the trial investigators and DSMC would consider stopping further enrollment. **Results:** 36 patients were enrolled on the TMT alone arm and 37 patients on the TMT + atezo arm. No grade 3 or higher colitis was reported in the atezo arm. Only one patient had treatment related grade 3 radiation cystitis which was diagnosed after finishing atezo treatment. No steroids were given. Overall 23 grade 3 or higher toxicity events were reported in the atezo arm vs 11 in non- atezo arm. Most common toxicity was hematological which was considered non-immune related. None of the grade 3 or higher toxicities were considered to be immune related by the treating investigator. **Conclusions:** There is no evidence of increased immune related grade 3-5 AEs.DSMC has recommended to continue enrollment. Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed Clinical trial information: NCT03775265. Research Sponsor: NIH/NCI grants CA180888, CA180819, CA180820, CA180821, CA180868, Pharmaceutical/Biotech Company.

Number of patients with a given type and grade of adverse event.

	Chemo + RT (n=36)						Chemo + RT + Atezo (n=37)					
	Grade						Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Acute kidney injury	35	0	0	1	0	0	35	0	0	2	0	0
Anemia	23	8	4	1	0	0	18	8	7	4	0	0
Hypokalemia	33	3	0	0	0	0	33	2	0	1	1	0
Lipase increased	36	0	0	0	0	0	36	0	0	0	1	0
Lymphocyte count decreased	30	0	0	4	2	0	30	0	1	4	2	0
Neutrophil count decreased	29	4	0	2	1	0	27	2	5	3	0	0
Platelet count decreased	21	11	3	1	0	0	16	18	2	1	0	0
Rash maculo-papular	36	0	0	0	0	0	34	2	0	1	0	0
Sepsis	36	0	0	0	0	0	36	0	0	0	1	0
Urinary tract infection	34	0	2	0	0	0	27	0	3	7	0	0
White blood cell decreased	28	2	3	2	1	0	22	6	2	7	0	0
MAX. GRADE ANY ADVERSE EVENT	2	8	15	8	3	0	0	6	8	18	5	0

An open-label, multicenter, phase IIIb study of patients with urinary tract carcinoma (UTC) (STRONG): Final analysis for fixed-dose durvalumab monotherapy (module A).

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Background: Patients (pts) with advanced UTC who fail first-line therapy have poor prognoses. Durvalumab (D; anti-PD-L1) 10 mg/kg every 2 weeks is approved for treatment of metastatic urothelial carcinoma (mUC) after progression on platinum-based chemotherapy (CT). Further understanding of long-term safety and efficacy of D in platinum and non-platinum pretreated pts, using a fixed dose every 4 weeks (Q4W), is of value. **Methods:** Module A of the phase IIIb STRONG study (NCT03084471) investigated the safety of fixed-dose D (1500 mg, Q4W) in pts with urothelial and nonurothelial UTC who progressed on or after platinum/non-platinum CT. The primary endpoint was the number of pts with adverse events of special interest (AESIs) – events with an inflammatory or immune-mediated mechanism that may require interventions (eg, steroids/immunosuppressants), including immune-mediated adverse events (imAE). AEs with onset date on or after the date of first dose and up to 90 days after study discontinuation were included. Secondary endpoints included serious AEs and overall survival (OS). Exploratory endpoints included objective response rate (ORR) and disease control rate (DCR) (investigator assessed per RECIST 1.1). **Results:** A total of 867 pts received D monotherapy. Median age was 68.1 yr and 80.0% were male; 87.1% had an ECOG PS 0-1 and 12.7% had ECOG PS 2. Most (96.3%) had urothelial UTC, including urothelial variants. Tumor PD-L1 expression was high (≥25%) in 239/577 (41.4%) pts with available data. Median treatment and follow-up duration were 12.1 wk (range 1-128) and 13.8 mo (range 0.0-28.8), respectively. Safety data are reported in the table. Deaths related to study treatment occurred in 9 pts (1.0%). At data cutoff (March 31, 2020), 30.8% of pts were in survival follow-up. Median OS was 7.0 mo (95% CI: 6.4-8.2); OS rate at 1 and 2 yr was 35.8% (95% CI: 32.5-39.2) and 20.2% (95% CI: 16.5-24.1), respectively. ORR was 17.7% with complete responses in 5.1% of pts. DCR at 6 mo was 33.0%. Median OS of subgroups: PD-L1 high or low: 9.3 mo (95% CI: 6.7-12.7) and 6.5 mo (95% CI: 5.8-8.1); ECOG PS 0-1 or 2: 8.4 mo (95% CI: 7.2–9.8) and 3 mo (95% CI: 2.0-4.1); urothelial and nonurothelial UTC: 7.0 mo (95% CI: 6.4-8.2) and 7.0 mo (95% CI: 2.7-10.2), respectively. **Conclusions:** Fixed-dose D monotherapy Q4W is convenient with an acceptable safety profile in previously treated pts for UTC. Long-term safety and efficacy data reported are consistent with published studies of D and other IO agents in this setting. Clinical trial information: NCT03084471. Research Sponsor: AstraZeneca.

	All AEs (%)	AESI (%)	TRAEs (%)	imAEs (%)
Any AE	787 (90.8)	438 (50.5)	407 (46.9)	97 (11.2)
Grade ≥3 AEs	365 (42.1)	69 (8.0)	78 (9.0)	17 (2.0)
Serious AEs	254 (29.3)	32 (3.7)	41 (4.7)	11 (1.3)
AE leading to discontinuation of treatment	77 (8.9)	18 (2.1)	33 (3.8)	10 (1.2)

TRAEs, Treatment-related AEs

Safety and efficacy of perioperative cisplatin/gemcitabine (cis/gem) and durvalumab (durva) for operable muscle-invasive urothelial carcinoma (MIUC): SAKK 06/17.

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Background: The combination of cisplatin-based chemotherapy with immune checkpoint inhibitors is extensively investigated in urothelial carcinoma. Using this combination in the neoadjuvant setting for patients (pts) with MIUC might improve pathological response rate (PaR: $<$ypT2N0) but carries the risk of increased perioperative morbidity. **Methods:** SAKK 06/17 is an open-label single arm phase II trial for pts with operable MIUC cT2-T4a cN0-1. Treatment consists of 4 cycles of neoadjuvant cis/gem q3w in combination with 4 cycles durva 1500mg q3w followed by resection. Durva is continued after surgery q4w for 10 cycles. Primary endpoint is event free survival (EFS) at 2 years. 58 pts are needed based on type I error of 10% and a power of 80% for H_1 EFS at 2 years $\geq$ 65% compared to H_0 EFS at 2 years $\leq$ 50%. We report the secondary endoints PaR, pathological complete remission (pCR: ypT0 N0), and safety on the full analysis set (FAS, received at least one dose of durva). **Results:** 61 pts were included between 7/18 and 9/19 at 12 sites. The FAS consists of 58 pts (79% male, median age 67.5 yrs) with bladder cancer (95%) or upper urinary tract/urethral cancer (5%). Clinical T2, T3, T4 stage were present at diagnosis in 69%, 21%, 10%, respectively, and 17% had cN1. 95% of pts received all 4 doses of neoadjuvant durva, 81% all 4 cycles of cis/gem and 17% switched to carboplatin. In total grade 3 and 4 adverse events (AE) during neoadjuvant treatment occurred in 48% and 27%, respectively. AEs related to durva were G3 in 7 pts (12%) and G4 in one patient (2%). Resection was performed in 53 pts (91%; 51 radical cystectomy, 2 nephroureterectomy), 4 pts refused surgery and one patient was irresectable due to a frozen pelvis. R0 resection was achieved in 52 pts (98%), one had R1. Postoperative complications included Clavien-Dindo III in 13 pts (24%) and IV in 5 pts (9%). PaR was found in 60% (95% CI 46.0%-73.5%) with 18 pts achieving pCR (34%; 95% CI 21.5%-48.3%) and 14 patients (26%) ypT1/ypTis. **Conclusions:** The first FAS results for neoadjuvant durvalumab in combination with cis/gem for operable MIUC confirm elevated pathological response rates and demonstrate acceptable safety. Postoperative morbidity is relevant but not exceeding the expected frequency or severity. Clinical trial information: NCT03406650. Research Sponsor: Swiss group for clinical cancer research SAKK.

Sapanisertib, a dual mTORC1/2 inhibitor, for *TSC1- or TSC2*-mutated metastatic urothelial carcinoma (mUC).

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Background: A mammalian target of rapamycin (mTOR) inhibitor, everolimus, showed activity in patients with metastatic urothelial carcinoma (mUC) including an exceptional objective response in a patient with a deleterious *TSC1* mutation. Sapanisertib is a potent inhibitor of mTOR complex 1 and 2. Here, we present the data from a phase II study of sapanisertib in patients with *TSC1*- or *TSC2*-mutated mUC. **Methods:** Eligible mUC patients with a *TSC1* or *TSC2* mutation received sapanisertib 3mg po daily on days 1 through 28 every 28 days. Primary endpoint was the overall response rate. Tumor samples were submitted for central confirmation of the mutation. A prescreening test for *TSC1/2* mutation was available at a central lab for those with unknown mutational status. **Results:** Tumor samples from 41 patients were submitted for either prescreening (n=24) or confirmation (n=17). Of 24 prescreening patients, 4 (16%) had TSC1 mutation; 2 (8%) had TSC2 mutations. Of 17 confirmatory testing, 16 were confirmed by the central lab. Of 23 potentially eligible patients with a *TSC1* or *TSC2* mutation, 17 (14 *TSC1*and 3 *TSC2*) were enrolled. Baseline characteristics of these 17 patients are shown. Four patients with *TSC1*- mutated mUC were deemed non-evaluable for response; two withdrew consent before starting sapanisertib to pursue an alternative therapy, and the other two withdrew consent with an adverse event before completing the first cycle. Of 13 evaluable patients, no objective response was observed. Although 4 patients had stable disease (SD) at their first restaging scan, none were confirmed to have SD with a subsequent scan. Median overall survival is 3.4 months. Four patients withdrew consent due to adverse event. Most common adverse events were hyperglycemia (80%), Cr elevation (53%) and AST increased (46.7%). No treatment-related death was observed. **Conclusions:** Sapanisertib did not result in any objective response in 13 patients with *TSC1*- or *TSC2*-mutated mUC. Given the lack of clinical activity, and problems with tolerance of sapanisertib, the trial was terminated early for futility. Future studies of an mTOR inhibitor or other targeted agent in the mTOR pathway should examine molecular alterations beyond *TSC1* or *TSC2*. Clinical trial information: NCT03047213. Research Sponsor: U.S. National Institutes of Health.

Baseline characteristics.

	N=17
Age, Median (Range)	67 (53-84)
Male	16 (94%)
Number of prior therapies, median (Range)	3 (1-6)
ECOG PS 0 or 1	15 (88%)
ECOG PS 2	2 (12%)

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

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Background: The renin-angiotensin system (RAS) is involved in regulation of angiogenesis, cell proliferation, desmoplasia and immunosuppression. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) may have antitumor effects partly by inhibiting transforming growth factor (TGF)-β, a major resistance mechanism in bladder cancer. **Methods:** Patients (pts) with muscle invasive bladder cancer (MIBC) treated or not treated with ACEi/ARB while receiving preceding radical cystectomy (RC) were assessed for pathologic complete response (pCR) defined as pT0N0 and overall survival (OS). Pathologic features, performance status, clinical stage, type and number of cycles of NAC, and presence of grade $\geq$3 toxicities were collected retrospectively. The Kaplan-Meier method was used to estimate overall survival (OS). Logistic and Cox regression was used to explore factors potentially prognostic for pCR and OS respectively. **Results:** 187 patients received NAC followed by RC. The mean age at the time of NAC was 65. 71% were male and 29% were female. Of the 187 patients, 61% received Cisplatin/Gemcitabine and 28.3% received dose dense MVAC. Of patients receiving NAC, 53 (28%) had a pCR. The 5-year OS was 64%. There were 41 (21.9%) patients taking an ACEi and 24 (12.8%) patients taking an ARB at the start of NAC. Of the 41 patients who took an ACEi, 17 (41.5%) had a pCR; of the 146 patients who did not take an ACEi, 36 (24.7%) had a pCR. ACEi intake during NAC was the only factor associated with pCR on multivariable analysis (odds ratio of 2.17 [95% CI 1.05-4.48] p = 0.037). pCR was the only factor shown to be associated with significantly improved OS (Hazard Ratio 0.18 [95% CI 0.07-0.45] p = $<$ 0.001). After adjusting for pCR, ACEi was not significantly prognostic of OS (HR = 1.12, 95% CI = 0.60 to 2.09, p = 0.72). ARB intake while receiving NAC was not associated with pCR or OS. **Conclusions:** ACEi intake was associated with significantly increased pCR in patients with MIBC receiving NAC, and pCR was the only significant factor associated with OS. We hypothesize that ACEi may augment the activity of NAC and increase pCR, which translates to improved OS. ACEi intake was not associated with improvement in OS potentially due to competing causes of mortality in patients requiring ACEi. Our data requires validation. Research Sponsor: None.

433 **Poster Session**

Single-arm phase II study of low-dose paclitaxel and pembrolizumab in platinum-refractory metastatic urothelial carcinoma (UC).

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Background: Single agent checkpoint inhibition is effective in a small proportion of platinum-refractory UC patients but improvements are needed. UC is highly inflammatory, and low-dose chemotherapy may enhance the response to immunotherapy. We evaluated whether combination therapy with low-dose paclitaxel and pembrolizumab is more efficacious than single-agent pembrolizumab which had an objective response rate (ORR) of 21% in a similar patient population in the KEYNOTE-045 study. We also incorporated multiple novel biomarker studies to explore immune regulatory mechanisms in UC. **Methods:** This is a prospective, single-arm phase II trial (NCT02581982) of pembrolizumab combined with low-dose paclitaxel in patients with platinum-refractory metastatic UC. Key inclusion criteria included measurable progression of disease within 12 months of platinum therapy and ECOG $\leq$1. Patients received pembrolizumab 200mg day 1 and paclitaxel 80 mg/m2 days 1 and 8 of a 21 day cycle for up to 8 cycles unless clinical or radiographic disease progression or unacceptable adverse events (AEs) were observed. Responding patients could remain on pembrolizumab maintenance for up to 2 years. The primary endpoint was ORR; key secondary endpoints included overall survival (OS), 6-month progression free survival (PFS), and safety. **Results:** Twenty-seven patients were treated between 4/2016 - 6/2020, with a median follow up of 9.9 months. At baseline, the median age was 68 years (range 49-80), with 81% men and 78% non-Hispanic white. The majority (59%) were ECOG 1. Twenty-one of 27 (78%) received prior definitive therapy: chemoradiation in 24% and surgery in 76%. The majority (78%) of patients received prior cisplatin. 70% progressed on a cisplatin-based regimen while 30% progressed on carboplatin-based regimen within 12 months of study entry. The ORR by intention to treat was 9 of 27 patients (33%) and in patients evaluable for response by imaging was 9 of 25 (36%), including 3 with complete response. Disease control rate in evaluable patients was 72%. Six-month PFS was 46.8% (95% CI: 27.2%, 64.2%) and median OS was 11.7 months (95% CI: 8.7 mo, NR). Common $\geq$ grade 2 AEs were anemia (44%), lymphopenia (37%), hyperglycemia (33%), and fatigue (33%). Possible treatment-related at least grade 3 or 4 AEs occurred in 56% of subjects, including 2 immune-mediated AEs (pneumonitis and nephritis) resulting in therapy cessation but a durable partial response. There were no grade 5 events. **Conclusions:** This study illustrates that the addition of low-dose paclitaxel to pembrolizumab improves outcomes in patients with platinum-refractory UC, relative to single-agent pembrolizumab. No unanticipated safety signals emerged. Exploratory analyses including PDL1 status, tumor mutational burden, and change in circulating microRNAs and in immune cell populations are ongoing. Clinical trial information: NCT02581982. Research Sponsor: Merck.

Atezolizumab (atezo) monotherapy versus chemotherapy in previously untreated locally advanced or metastatic urothelial carcinoma (mUC): Clinical outcomes by PD-L1 status in cisplatin (cis)-ineligible pts from the phase III IMvigor130 study.

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Background: Atezo (anti–PD-L1) monotherapy is approved for cis-ineligible pts who have locally advanced or mUC with PD-L1–expressing immune cells on ≥ 5% of the tumor area (IC2/3 per VENTANA SP142 IHC assay). The IMvigor130 primary analysis demonstrated a significant PFS benefit with atezo + platinum/gemcitabine (plt/gem) (arm A) vs placebo (pbo) + plt/gem (arm C) as 1L treatment for mUC (Galsky *Lancet* 2020); at that time, interim OS data for arm A vs C were encouraging but immature. OS with atezo monotherapy (arm B) could not be formally tested, but favorable efficacy was seen in IC2/3 pts. In this exploratory analysis, we assess outcomes by PD-L1 status in cis-ineligible pts. **Methods:** Pts were randomized 1:1:1 to arms A, B or C (Galsky *Lancet* 2020). Evaluation of OS (co-primary EP) was performed via a hierarchical fixed sequence procedure: arm A vs C ITT pts; then, arm B vs C ITT and IC2/3 pts. No formal testing was performed in this exploratory subgroup analyses; OS and RECIST 1.1 ORR (per investigator [secondary EP]) were descriptively evaluated. **Results:** Efficacy data suggested OS and ORR benefit in atezo-treated cis-ineligible IC2/3 pts (Table). In the overall safety population, all-grade treatment-related AEs (TRAEs) had occurred in 60% and 96% of arm B and C pts, respectively; grade 3-4 TRAEs occurred in 15% and 81%, respectively. Biomarker data evaluating PD-L1 biology (assessed by SP142) and associated transcriptome analysis in arms B vs C will be presented. **Conclusions:** This exploratory analysis of IMvigor130 pts with 1L cis-ineligible IC2/3 mUC provides additional evidence for clinical benefit with single-agent atezo, a well-tolerated treatment with a distinct safety profile vs chemo. Analyses with longer OS follow-up are warranted. Clinical trial information: NCT02807636. Research Sponsor: F. Hoffmann-La Roche Ltd.

	OS events/ pts (arm B)	OS events/ pts (arm C)	Outcome	Arm B	Arm C	OS HR (95% CI)
ITT	191/360	198/359	mOS (95% CI), mo	15.7 (13.1, 17.8)	13.1 (11.7, 15.1)	1.02 (0.83, 1.24)[a]
–	–	–	ORR (95% CI), %	23 (19, 28)	43 (38, 49)	–
IC2/3	33/88	42/85	mOS (95% CI), mo	NE (17.7, NE)	17.8 (10.0, NE)	0.68 (0.43, 1.08)[a]
–	–	–	ORR (95% CI), %	39 (28, 50)	44 (33, 55)	–
Cis-ineligible[b] IC2/3	21/50	26/43	mOS (95% CI), mo	18.6 (13.1, NE)	10.0 (7.4, 19.1)	0.53 (0.30, 0.94)[c]
–	–	–	ORR (95% CI), %	38 (25, 53)	33 (19, 49)	–
Cis-ineligible[b] IC0/1[d]	85/140	85/140	mOS (95% CI), mo	11.2 (6.9, 15.0)	11.2 (9.9, 15.0)	1.11 (0.82, 1.51)[c]
–	–	–	ORR (95% CI), %[e]	16 (10, 23)	42 (34, 51)	–

mFU, 11.8 mo; data cutoff May 31, 2019. NE, not estimable. [a] Stratified per randomization stratification factors: PD-L1 status (ITT only), Bajorin risk factor score/liver mets, investigator's choice of plt (cis or carboplatin); Galsky *Lancet* 2020. [b] Per Galsky *Lancet Oncol* 2011, excluding NYHA classification. [c] Unstratified. [d] IC0/1 = PD-L1 IC < 5%. [e] ORR for cis-ineligible IC0/1 pts based on n = 139 in each arm.

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Post-hoc analysis of long-term outcomes in patients with CR, PR, or SD to pembrolizumab (pembro) or platinum-based chemotherapy (chemo) as 1L therapy for advanced urothelial carcinoma (UC) in KEYNOTE-361.

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Background: The phase III KEYNOTE-361 study compared efficacy and safety of 1L pembro + chemo or pembro vs chemo in pts with advanced UC. The trial did not meet its primary endpoints of PFS or OS superiority for pembro + chemo vs chemo; formal testing for OS for pembro vs chemo was not performed. We present a post hoc landmark analysis to examine the durability of CR/PR/SD and long-term survival in pts with CR, PR, or SD to pembro vs chemo at week 9 in KEYNOTE-361 (NCT02853305). **Methods:** Landmark analyses of OS by CR/PR/SD at 9 weeks after randomization in the ITT population were performed. Pts were included if they had a best response of CR/PR/SD per RECIST v1.1 by blinded independent central review at the landmark date of week 9 (first imaging assessment per study protocol). Duration of CR/PR/SD and OS were estimated by the Kaplan-Meier method. No formal comparisons were performed. **Results:** 307 pts were randomized to receive pembro and 352 pts to receive chemo in the KEYNOTE-361 study. As of Apr 29, 2020, the median (range) time from randomization to data cutoff was 32.5 (22.0-42.4) mo for the pembo arm and 31.4 (22.1-41.6) mo for the chemo arm. In the landmark analysis, fewer pts had CR/PR/SD at week 9 with pembro (n=137 [45%]) than with chemo (n=253 [72%]). Median (range) duration of response for pembro vs chemo was 18.7 (4.4+-35.4+) vs 12.3 (0.0+-29.7+) mo for pts with CR, and 35.0 (1.1-36.1+) vs 6.1 (0.0+-36.3+) mo for pts with PR. Median (range) duration of SD was 4.8 mo (0.0-38.2+) with pembro and 4.6 mo (0.0-16.1+) with chemo. Median OS (95% CI) for pembro vs chemo was not reached (NR) (25.5-NR) vs NR (19.1-NR) for pts with CR; NR (NR-NR) vs 14.8 mo (12.1-21.0) for pts with PR; and 18.5 mo (13.8-28.8) vs 11.1 mo (8.1-14.6) for pts with SD, respectively. Long-term OS rates were higher with pembro vs chemo across all groups (CR/PR/SD) at week 9 (Table). **Conclusions:** In this post hoc landmark analysis, chemo was associated with more initial responses than pembro, whereas pembro was associated with longer median duration of CR and PR, and generally longer median OS than chemo. Among pts who achieved CR/PR/SD at week 9, the relative OS benefit for pembro vs chemo increased over time. Clinical trial information: NCT02853305.Research Sponsor: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

OS rate by CR/PR/SD from week 9.

	Pembro Arm (N=137)			Chemo Arm (N=253)		
	CR (n=16)	PR (n=54)	SD (n=67)	CR (n=25)	PR (n=127)	SD (n=101)
6 mo, %	100	98.1	85.1	100	90.6	72.3
(95% CI)	(100-100)	(87.6-99.7)	(74.0-91.7)	(100-100)	(84.0-94.5)	(62.4-79.9)
12 mo, %	93.8	86.9	65.4	80.0	59.8	46.5
(95% CI)	(63.2-99.1)	(74.5-93.5)	(52.6-75.5)	(58.4-91.1)	(50.8-67.8)	(36.6-55.9)
18 mo, %	93.8	79.4	51.7	76.0	45.7	33.7
(95% CI)	(63.2-99.1)	(65.8-88.0)	(39.1-62.9)	(54.2-88.4)	(36.8-54.1)	(24.7-42.9)
24 mo, %	87.5	73.6	43.8	57.1	33.9	21.1
(95% CI)	(58.6-96.7)	(59.5-83.4)	(31.6-55.3)	(34.2-74.6)	(25.7-42.3)	(13.7-29.7)

Preliminary analysis of a phase II, multicenter, randomized, active-control study to evaluate the efficacy and safety of eganelisib (IPI 549) in combination with nivolumab compared to nivolumab monotherapy in patients with advanced urothelial carcinoma.

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Background: Inhibition of the PD-1 pathway has demonstrated clinical benefit in metastatic urothelial carcinoma (mUC); however, response rates of 15% to 29% highlight the need for more effective therapies, especially for PD-L1- patients. Eganelisib is a first-in-class, novel, oral agent which selectively inhibits PI3K-γ, with the goal of improving the immune response to checkpoint inhibitors (CPI). **Methods:** Eligible patients (pts) with mUC who progressed on > 1 platinum-based chemotherapy regimen and were CPI naïve were enrolled. Pts were randomized 2:1 to receive eganelisib in combination with nivolumab (EN) or placebo with nivolumab (PN). Pts were stratified by baseline circulating monocytic myeloid derived suppressor cells (mMDSC) level. The primary endpoint was objective response rate (ORR) per RECIST v1.1 in pts with high baseline mMDSC levels. Other endpoints included ORR, progression free survival (PFS) and overall survival (OS) in all pts and PD-L1 +/- pts. **Results:** We report preliminary data (as of 9/1/2020) for the first 49 pts with 33 randomized to receive EN and 16 PN. Preliminary ORR/PFS is presented in the table below. Except for the mMDSC high subgroup, ORR and PFS were improved in the EN arm compared to the PN arm. The duration of exposure was a median of 15 weeks for EN and 11 for PN. Most common all-Gr AEs (EN vs PN %) were pyrexia (33 vs 0), decreased appetite (30 vs 19), pruritis (24 vs 6), rash (24 vs 6), asthenia (21 vs 31), and transaminase elevation (21 vs 6). Most common Gr≥3 AEs (EN vs PN %) include hepatotoxicity (15 vs 0), transaminase elevation (12 vs 6), and rash (9 vs 0). Following an early safety review, eganelisib dose was reduced from 40 to 30 mg, resulting in a reduction of hepatic AEs. **Conclusions:** Preliminary data demonstrates that the combination of eganelisib, once reduced to 30 mg, and nivolumab was well tolerated with hepatic and skin-related toxicities more common in the EN arm. When compared to PN, the combination demonstrated an improved ORR and PFS, especially in the PD-L1- subset. Updated efficacy, including PFS and OS, safety and translational data will be presented. Clinical trial information: NCT03980041. Research Sponsor: Infinity Pharmaceuticals.

ORR n of N (%) [95% CI]	Eganelisib + Nivolumab	Nivolumab + Placebo
All Patients	10 of 33 (30.3) [16,49] *	4 of 16 (25.0) [7, 52]
mMDSC ≥ 22.3	0 of 7 (0)	1 of 3 (33.3) [1, 91]
mMDSC < 22.3	10 of 26 (38.5) [20,59]*	3 of 13 (23.1) [5, 54]
PD-L1+ (TPS > 1%)	4 of 5 (80.0) [28,100]	2 of 4 (50.0) [7, 93]
PD-L1- (TPS < 1%)	6 of 23 (26.1) [10, 48]*	1 of 7 (14.3) [0, 58]
Pts with ≥Gr3 treatment-related hepatic AEs	6 of 12 (50.0) [21, 79]*	0 of 0

PFS median weeks [95% CI]	Eganelisib + Nivolumab	Nivolumab + Placebo	HR estimated Cox Regression
All Patients	9.1 [8.0, NE]	8.0 [7.9, 16.4]	0.79 [0.39, 1.60]
PD-L1-	9.1 [8.0, NE]	7.9 [2.4, 8.0]	0.50 [0.19, 1.32]

* 2 patients with pseudo progression (uPD followed by cPR)

437 **Poster Session**

Derazantinib (DZB) in combination with atezolizumab (AZB) in patients with solid tumors: Results from the dose-finding phase Ib substudy of FIDES-02.

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Background: DZB is an oral small-molecule FGFR1/2/3 kinase inhibitor, which demonstrated antitumor activity in preclinical and clinical studies (in cholangiocarcinoma patients [pts] with FGFR2-driven tumors and in FGFR1-3-driven urothelial cancer [UC] PDX models). In CSF1-stimulated mouse bone-marrow derived macrophages, DZB reduced CSF1R phosphorylation with a maximal effect similar to the selective CSF1R inhibitor BLZ945, suggesting DZB could have an effect on tumor-associated macrophage regulation. Thus, DZB+AZB is a rationale combination to be investigated in immunogenic and FGFR-driven tumors like UC. **Methods:** FIDES-02 is a multi-cohort open-label Phase 1b/2 study evaluating the effect of DZB as monotherapy and DZB+AZB in combination. To determine the RP2D of DZB+AZB, a total of 26 pts with UC (N = 4) and other solid tumors (N = 22), of whom 7 pts carried various *FGFR* genetic aberrations (GA), were enrolled at 2 dose levels (DL) (1200 mg AZB Q3W + 200 mg [DL1] / 300 mg [DL2] DZB QD) and treated until disease progression or unacceptable toxicity. Both DLs were divided into MTD (endpoint: dose-limiting toxicity [DLT] at D21) and expansion cohorts to investigate both acute and delayed adverse events (AEs) per CTCAE v5. **Results:** In the MTD cohorts of both DL1 (N = 7) and DL2 (N = 6) no DLTs were observed, and the DL1 and DL2 expansion cohorts subsequently enrolled 7 and 6 pts, respectively. The most frequent treatment-emergent AEs across both DLs were fatigue (31%), nausea (27%), diarrhea (23%), the most frequent laboratory abnormalities were increased ALT (58%), and AST (50%). Non-DLT grade (G) $\geq$ 3 treatment-related AEs (TRAE) across both DLs were G3 diarrhea (4%), G3 nausea (4%), G3 asthenia (4%), oral fungal infection (4%) and one case of immune-related G4 nephritis (4%). Dose interruptions / reductions and discontinuations due to TRAEs occurred in 19% and 8%, respectively. Pharmacokinetic analyses demonstrated that DZB exposure parameters and AZB serum concentrations in pts treated with DZB+AZB were similar to those assessed in pts under DZB / AZB monotherapy. At data cut-off, 2 of 14 (DL1) and 7 of 12 pts (DL2) were still on treatment. Median duration of treatment in DL1 was 9.7 weeks (range, 9-25), and best overall response per investigator assessment was SD in 4 of 10 efficacy-evaluable DL1 pts. DL2 efficacy analysis was uninformative at cutoff. The combination of 1200 mg AZB Q3W with both 200 mg and 300 mg QD DZB was found to be safe and tolerable. **Conclusions:** The combination of DZB+AZB is safe at both investigated DLs, the RP2D has been determined as 300 mg DZB QD+1200 mg AZB Q3W. DZB can be safely dosed at its monotherapy RP2D in this novel combination with AZB. The anti-tumor efficacy of DZB+AZB is currently being investigated in adequately designed cohorts of FIDES-02 with enrichment for UC pts with *FGFR* GA. Clinical trial information: NCT04045613. Research Sponsor: Basilea Pharmaceutica International Ltd.

Avelumab (Ave) first-line (1L) maintenance plus best supportive care (BSC) versus BSC alone for advanced urothelial carcinoma (UC): JAVELIN Bladder 100 subgroup analysis based on duration and cycles of 1L chemotherapy.

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Background: Avelumab 1L maintenance is approved in the United States for patients with advanced UC that has not progressed with 1L platinum-containing chemotherapy based on significantly prolonged overall survival (OS) vs BSC seen in the phase III JAVELIN Bladder 100 trial (NCT02603432). However, optimal duration of 1L chemotherapy is unknown and some patients are unable to receive 6 cycles. We report a post hoc analysis of efficacy by duration or number of cycles of 1L chemotherapy. **Methods:** Eligible patients with unresectable locally advanced or metastatic UC that had not progressed with 4-6 cycles of 1L gemcitabine + cisplatin or carboplatin were randomized to receive maintenance avelumab + BSC or BSC alone within 4-10 weeks. Subgroups were defined by quartiles (Qs) for duration (<Q1 [<15.0 weeks], Q1-Q2 [15.0 to <18.0 weeks], Q2-Q3 [18.0 to <20.1 weeks], and >Q3 [>20.1 weeks]) or estimated number of cycles (4, 5, or 6) of 1L chemotherapy. Duration of chemotherapy included dosing delays/interruptions, and the decision to stop 1L chemotherapy was at the investigator's discretion. Treatment arms were compared using an unstratified Cox proportional hazards model for OS. The potential impact of baseline characteristics on treatment patterns or dose intensity was not explored. **Results:** Numbers of patients in 1L chemotherapy subgroups were generally well balanced between arms (Table). An OS benefit was observed for avelumab + BSC vs BSC alone across subgroups with differing durations or cycles of 1L chemotherapy (Table). A progression-free survival benefit was also observed for avelumab + BSC vs BSC alone across subgroups. No significant treatment-by-cycle interaction (at 0.05 level) was observed. **Conclusions:** Improved OS was observed with avelumab 1L maintenance vs BSC alone irrespective of duration or cycles of 1L chemotherapy received prior to entering the trial. Among patients who stopped 1L chemotherapy prior to 6 cycles, avelumab 1L maintenance still provided an OS benefit. Clinical trial information: NCT02603432. Research Sponsor: Pfizer Inc, Pharmaceutical/Biotech Company.

	Avelumab + BSC, events/ patients	BSC alone, events/ patients	mOS with avelumab + BSC (95% CI), months	mOS with BSC alone (95% CI), months	HR (95% CI)
Duration					
<Q1	34/85	45/86	18.9 (15.4, NE)	13.0 (10.3, 18.7)	0.65 (0.418, 1.021)
Q1-Q2	34/73	37/72	19.9 (13.6, NE)	15.5 (10.7, 21.0)	0.79 (0.499, 1.267)
Q2-Q3	45/100	56/111	19.2 (16.7, NE)	14.3 (12.7, 19.4)	0.74 (0.499, 1.096)
>Q3	32/92	40/79	24.0 (20.6, NE)	17.9 (11.6, NE)	0.63 (0.394, 1.003)
Cycles*					
4	54/127	62/124	19.9 (17.7, NE)	13.7 (11.4, 19.4)	0.69 (0.481, 1.000)
5	24/54	27/59	19.9 (15.1, NE)	17.8 (11.8, NE)	0.98 (0.568, 1.707)
6	63/150	80/148	24.0 (18.9, NE)	14.0 (12.1, 19.6)	0.66 (0.472, 0.915)

HR, hazard ratio; m, median months from randomization (after chemotherapy); NE, not estimable * Derived using exposure records of 1L chemotherapy based on a 21-day cycle assumption.

Impact of subsequent therapy on survival in KEYNOTE-361: Pembrolizumab (pembro) plus chemotherapy (chemo) or pembro alone versus chemo as first-line therapy for advanced urothelial carcinoma (UC).

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Background: The phase III KEYNOTE-361 study examined the efficacy and safety of 1L pembro + chemo or pembro alone vs chemo for pts with advanced UC. The PFS and OS benefit of pembro + chemo vs chemo did not reach statistical significance; no further formal tesing was done. We present an exploratory analysis of OS by subsequent therapy in KEYNOTE-361 (NCT02853305) to assess how 1L and 2L therapy selection affected survival outcomes; no formal comparisons were conducted. **Methods:** OS was estimated for pts by whether they received subsequent therapy, and by whether subsequent therapy included an anti–PD-(L)1 agent. **Results:** 351 pts were randomized to pembro + chemo, 307 pts to pembro, and 352 pts to chemo. As of Apr 29, 2020, the median (range) time from randomization to data cutoff was 31.7 (22.0-42.3) mo. 124/351 pts (35%) in the pembro + chemo arm, 126/307 pts (41%) in the pembro arm, and 215/352 pts (61%) in the chemo arm received any subsequent therapy. Similar rates of subsequent therapy (pembro + chemo: 32%; pembro: 43%; chemo: 59%) were observed for pts who experienced progressive disease (PD) by blinded independent central review (BICR). A higher rate of pts (169/352 [48%]) in the chemo arm received subsequent anti–PD-(L)1 therapy than in either the pembro + chemo arm (23/351 [7%]) or pembro arm (14/307 [5%]). Due to the small pt numbers, pts in the pembro + chemo or pembro arms who received subsequent anti—PD-(L)1 were not considered further. This analysis included all pts who received 2L therapy (465/1010 pts [46%]); the rate of 2L therapy was similar in pts with PD by BICR (274/615 [45%]). Chemo agents alone or in combination, specifically carboplatin, cisplatin, docetaxel, doxorubicin, gemcitabine, and paclitaxel, were the most commonly received subsequent therapies for pts who did not receive anti–PD-(L)1 in 2L. Pts who received 1L chemo followed by subsequent anti–PD-(L)1 had longer mOS (19.1 mo [95% CI 16.2-22.2]) than pts with 1L pembro followed by 2L therapy not including an anti—PD-(L)1 agent (16.0 mo [95% CI 11.8-19.2]) (Table). **Conclusions:** In this exploratory analysis, favorable survival outcomes were observed for pts who received 1L chemo followed by anti–PD-(L)1 compared with pts who received 1L pembro followed by 2L therapy not including an anti–PD-(L)1 agent. These data underline the continued importance of immunotherapy as 2L therapy for advanced UC. Clinical trial information: NCT02853305. Research Sponsor: Merck & Co., Inc.

	mOS, mo (95% CI) by subsequent therapy		
Arm (n/n/n)	**Anti–PD-(L)1**	**Not including anti–PD-(L)1**	**None**
Pembro + Chemo (23/101/227)	[a]	18.2 (15.8-20.6)	13.2 (11.6-17.4)
Pembro (14/112/181)	[b]	16.0 (11.8-19.2)	13.6 (8.1-17.9)
Chemo (169/46/137)	19.1 (16.2-22.2)	14.9 (11.7-18.8)	9.4 (7.6-10.6)

[a] Based on small pt number (n=23); mOS (95% CI) was 29.3 mo (24.1-34.2). [b] Based on small pt number (n=14); mOS (95% CI) was 30.8 mo (14.8-35.7).

Phase II open-label study of S-588410 as maintenance monotherapy after first-line platinum-containing chemotherapy in patients with advanced or metastatic urothelial carcinoma.

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Background: S-588410 is a cancer peptide vaccine composed of 5 human leukocyte antigen (HLA)-A*24:02-restricted epitope peptides derived from 5 cancer-testis antigens: DEPDC1, MPHOSPH1, URLC10, CDCA1 and KOC1; all of which are highly expressed in urothelial carcinoma. This study aimed to evaluate the effect of S-588410 maintenance therapy on peptide-specific cytotoxic T-lymphocyte (CTL) induction in patients with advanced or metastatic urothelial carcinoma after first-line platinum-based chemotherapy. **Methods:** An open-label, multicenter phase II trial was performed across 62 sites in Japan, the United Kingdom, France and Bulgaria (EudraCT 2013-005274-22). Eligible patients had completed ≥4 cycles of first-line platinum-based chemotherapy without disease progression. HLA-A*24:02-positive patients received S-588410 (1 mg of each of 5 peptides mixed with Montanide ISA 51 VG) subcutaneously weekly for 12 weeks, then every 2 weeks for up to 2 years. HLA-A*24:02-negative patients were enrolled in an observation group and did not receive study drug. The primary endpoint for the S-588410 group was the CTL induction rate at 12 weeks, defined as the proportion of patients who showed increased CTL activity for ≥1 peptide. Secondary endpoints included CTL induction rate after 1 year, antitumor effect defined by immune-related response criteria, progression-free survival (PFS), overall survival (OS), and safety. **Results:** A total of 81 patients with platinum-sensitive advanced or metastatic urothelial carcinoma were enrolled (S-588410 group, n=45; observation group, n=36) between April 2014 and November 2017. Most patients were male and Asian with a mean age of 67 years. CTLs were induced in 42 (93.3%) patients who received S-588410 for 12 weeks ($P<0.0001$, one-sided binomial test where the CTL induction rate is ≤50% as the null hypothesis). The CTL induction rate steadily increased to 95.6% within 48 weeks. CTL activity was high for the DEPDC1, MPHOSPH1 and URLC10 peptides. The response rate (immune-related complete response [CR] or partial response [PR]) was 8.9% (4/45 patients) in the S-588410 group and 0% in the observation group. Tumor imaging showed gradual (PR, n=3) and durable (CR, n=1) tumor shrinkage after ≥36 weeks in the S-588410 group. Median PFS was 18.1 weeks in the S-588410 group and 12.5 weeks in the observation group. Median OS was 71 and 99 weeks, respectively. The most frequent treatment-emergent adverse event was injection site reaction (42/45 patients [93.3%]; Grades 1–3). Pyrexia, rash and pruritus were also observed in the S-588410 group, but not the observation group. **Conclusions:** S-588410 showed a potent immune response and acceptable safety profile in patients with advanced or metastatic urothelial carcinoma, potentially offering a clinical benefit as post-chemotherapy maintenance therapy. Clinical trial information: EudraCT 2013-005274-22. Research Sponsor: Shionogi & Co., Ltd.

Identification of characteristics associated with long-term survival in patients with metastatic urothelial carcinoma (mUC) who received durvalumab (D) with or without tremelimumab (T) in clinical studies.

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Background: Immune checkpoint inhibitors (ICI) have changed the landscape of mUC, yet outcomes are variable as some patients (pts) do not respond to treatment while others have a durable response. To optimally select pts who may derive benefit from ICIs, predictive factors are required. This retrospective, post-hoc analysis evaluated pt characteristics to determine differences between short and long-term survivors among pts with mUC who received D (anti–PD-L1) with or without T (anti–CTLA-4) in two clinical studies. **Methods:** Pts with platinum-refractory mUC who received D monotherapy in the phase I/II study 1108 (10 mg/kg Q2W, up to 12 mo) or D+T in the phase I study 10 (D at 20 mg/kg + T at 1 mg/kg Q4W for 4 mo, then D at 10 mg/kg Q2W for 12 mo) were included. Pt characteristics, tumor characteristics, radiological assessments, and biological assessments were collected. The primary outcome measure was long-term overall survival (OS). Pts were categorized as OS ≥2 yrs (from 1st dose of study drug) or OS <2 yrs. A univariate analysis was conducted on each baseline characteristic to assess independent associations with long-term OS; a multivariate logistic regression model was employed including each variable with a p-value ≤0.1 as factors or covariates. **Results:** A total of 367 pts with mUC were included in the analysis: 88 (24.0%) had OS ≥2 yrs (range: 2.09–4.99) and 279 (76.0%) had OS <2 yrs (range: 0.03–1.98). Pts with OS ≥2 yrs had a significantly higher objective response rates than those with OS <2 yrs (71.6% vs 5.7%; p<0.0001) and a significantly longer duration of response (median 2.3 yrs vs 0.39 yrs; p<0.0001). The characteristics included in the multivariate logistic regression model are listed in the Table. Long-term OS was significantly associated with ECOG PS, PD-L1 status, baseline hemoglobin level, and baseline absolute neutrophils count. **Conclusions:** Our analyses show that several characteristics, including tumor response to treatment, are associated with long-term OS for pts with mUC treated with D or D+T. Further investigation into these and other characteristics may provide additional insights into long-term survival outcomes with ICIs. Research Sponsor: Astra-Zeneca.

Baseline characteristics (bold = reference)	Univariate: P-value	Multivariate: Odds Ratio (95% CI); P-value
Sex (female/male)	0.042	1.65 (0.76–3.55); 0.203
ECOG PS (0 vs 1/2)	<0.0001	2.11 (1.12–3.99); 0.022
PD-L1 Status (low/neg vs high)	0.002	1.90 (1.00–3.61); 0.049
Lymph node only disease (absent/present)	<0.0001	0.76 (0.27–2.15); 0.611
Visceral disease (absent/present)	<0.0001	2.30 (0.96–5.54); 0.063
Time from initial diagnosis to study entry	0.042	1.16 (0.80–1.68); 0.443
Hemoglobin level	<0.0001	1.48 (1.18–1.86); 0.001
Lactate dehydrogenase level	0.003	0.75 (0.39–1.42); 0.371
Absolute neutrophils count	<0.0001	0.43 (0.19–0.98); 0.045

Phase II trial of escalating doses of neoadjuvant atezolizumab for patients with non-metastatic urothelial carcinoma ineligible for cisplatin-based neoadjuvant chemotherapy.

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Background: For patients (pts) with muscle-invasive bladder cancer (MIBC) who are ineligible for cisplatin-based chemotherapy (cisplatin), the standard of care option is radical cystectomy (RC) alone. This prospective clinical trial investigated the safety and efficacy of escalating doses of atezolizumab (ATZ) as neoadjuvant therapy prior to RC in pts with non-metastatic urothelial cancer. **Methods:** This single-arm, single institution, phase II trial investigated the administration of one (n = 6), two (n = 5) or three (n = 9) cycles of ATZ (1200 mg IV given every 3 weeks) in pts with MIBC who are either ineligible for or refused cisplatin prior to RC. Key inclusion criteria were urothelial carcinoma of the bladder (T2-T4a,N0-1,M0) and inability to receive cisplatin-based treatment (eGFR $<$ 60 mL/min, G$\geq$2 neuropathy/hearing loss, pt decision). Pts with high-risk disease ($>$ pT2 or LN+) at the time of RC were eligible to receive adjuvant ATZ for up to 16 total cycles. Primary efficacy endpoint was pathologic complete response (pCR; pT0N0). Important secondary endpoints were safety of treatment, rates of pathologic downstaging and biomarker assessments in serial tissue samples. Pts were followed for up to 2 years following RC. **Results:** Among 20 pts with MIBC, median age was 69 (range 61-81) and 75% were male. Most commonly pts were cisplatin-ineligible due to low GFR (35%), hearing loss (25%) or neuropathy (10%); remainder refused cisplatin (30%). At trial enrollment, pT2, pT3, and pT4 was present in 80%, 15%, and 5% of pts and 10% had enlarged pelvic lymph nodes ($>$ 10 mm) on scans. All pts completed intended treatment cycles and all had RC within the defined timeframe ($>$ 3 weeks from last and $<$ 12 weeks from first treatment). pCR at RC was 10% (2/20 pts), and was observed in pts receiving 1 and 2 cycles of ATZ. Pathologic downstaging ($\leq$pT1N0) was achieved in 25% (5/20 pts) and observed across all three dose levels. Adjuvant ATZ was given to 8 pts. TRAEs of any grade during perioperative period occurred in 75% and G3 TRAEs in 10% (diarrhea, fecal incontinence). There were no G4 or G5 events. Median follow-up from the time of RC was 21.4 months at the time of data cutoff in 10/2020. Among evaluable pts, 1-year RFS and OS were 71% and 94% while 2-year RFS and OS were 64% and 75%. **Conclusions:** This prospective trial supports the safety and efficacy of ATZ as neoadjuvant therapy in MIBC. Although pCR and rates of downstaging were lower than what was previously reported in comparable neoadjuvant trials of checkpoint inhibitors in MIBC, pCRs in this trial were seen even in pts receiving only 1-2 doses of ATZ. Many pts had a durable recurrence-free period and all 4 evaluable pts who had pathologic downstaging were alive and disease free at 2 years post RC. Translational and biomarker work from this study is also being pursued. Clinical trial information: NCT02451423. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/ Biotech Company.

Efficacy of enfortumab vedotin in advanced urothelial cancer: Retrospective analysis of the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) Study.

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Background: Enfortumab vedotin (EV) is an antibody-drug conjugate targeting Nectin-4, which is FDA approved for patients (pts) with treatment-refractory advanced urothelial cancer (aUC). The activity of EV in pt subsets of interest such as those with distinct histological variants has not been well defined. **Methods:** A retrospective study of pts with aUC treated with ≥1 dose of EV as standard of care (SOC) or on a clinical trial (if trial results already reported) at 12 US sites was undertaken. Objective response rate (ORR) was investigator-assessed for pts with at least one post-baseline scan or clear evidence of clinical progression. ORR was compared across subsets of interest using proportion test. **Results:** A total of 184 patients with aUC were included; median age at diagnosis 70, 20% women and 60% with definitive surgery. Most common primary sites included bladder (70%) and upper tract (28%). Majority of pts (72%) had pure urothelial histology (UH) per local review, but 26% had at least a component of variant histology (VH), most commonly squamous (14%), micropapillary (8%) or plasmacytoid (3%). EV was given as monotherapy in 84% and as SOC in 58%; and 81% had ≥ 1 prior treatment in the metastatic (met) setting. ECOG PS was ≥2 in 15%; 37% had baseline neuropathy, 15% diabetes and 9% had GFR≤30. At median follow-up of 37.0 (IQR: 20.5-60.2) months from initial diagnosis, median time from met diagnosis to EV start was 11.7 (IQR: 4.3 – 20.5) months. Median duration of EV was 5.5 (IQR: 1.4 – 6.7) months, and 84% of pts were evaluable for response. ORR for evaluable pts was 53% (8% CR, 45% PR); 25% had SD and 21% PD. Median PFS and OS were not yet reached. At data cutoff in 9/2020, 55% had stopped EV (36% due to PD, 19% intolerance) and 65% were alive. Comparison of ORR in subgroups of interest for 127 evaluable pts treated with EV monotherapy is shown in the table below. Notably, among 31 pts with FGFR3 alterations, 26 were evaluable and ORR was 46%. **Conclusions:** In a large, retrospective, multi-institutional cohort, responses to EV were observed across a broad range of aUC pts, including pts with variant histology component, FGFR3 alterations and also in populations previously excluded from clinical trials such as pts with GFR<30 and significant baseline comorbidities. No significant differences in ORR were demonstrated for patient subsets of interest. Research Sponsor: None.

Subgroups	Total Pt No.	ORR % (95% CI)	p value
UH	87	56 (46, 66)	0.2
VH	38	42 (28, 58)	
Bladder	90	52 (42, 62)	0.98
Upper Tract	36	50 (34, 66)	
Primary Surgery or ChemoRT	79	49 (39, 60)	0.61
None	41	56 (41, 70)	
LN Only	17	35 (17, 59)	0.27
Non-Liver Visceral Mets	72	54 (43, 65)	
Liver Mets	36	58 (42, 73)	
ECOG 0/1	111	52 (43, 61)	1
ECOG 2/3	16	50 (28, 72)	
Neuropathy	52	63 (50, 75)	0.06
No Neuropathy	74	45 (34, 56)	
Diabetes	20	55 (34, 74)	0.96
No Diabetes	107	51 (42, 61)	
GFR > 60	52	50 (37, 63)	0.74
GFR 30-60	61	56 (43, 67)	
GFR <= 30	13	46 (23, 71)	

Association between prior radical surgery (RS) and outcomes with immune checkpoint inhibitor (ICI) therapy for advanced urothelial carcinoma (aUC).

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Background: It is unclear whether prior RS of primary tumor is associated with response and outcomes with ICI in aUC. We hypothesized that such response and outcomes would not differ based on prior RS. **Methods:** We performed a retrospective cohort study including patients (pts) with aUC who received ICI. We compared overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) between pts with vs without RS [cystectomy or (nephro)-ureterectomy]. Analysis was stratified based on ICI therapy line (first-line vs salvage). A separate comparison between pts with prior RS or radiation (RT) only or none was also pursued. ORR was compared between groups using logistic regression, as well OS and PFS using cox regression analysis; a multivariable model was built adjusting for calculated Bellmunt score. $P<0.05$ was significant. **Results:** We identified 984 pts from 24 institutions; 682, 704 and 673 were included in OS, PFS and ORR analyses, respectively; 54% of pts had prior RS with median age 68 at ICI initiation with RS vs 71 without RS with similar proportion of men (73-74%) and ever smokers (70-71%). The RS group had higher proportion (%) of white pts (77% vs 71%), lower % of pts with Hb<10g/dL at ICI initiation (23% vs 32%) but not significantly higher % of liver metastasis at ICI initiation (23% vs 17%). Bellmunt score with vs without RS was 16% vs 11%, 50% vs 48%, 27% vs 37%, 7% vs 4% for 0, 1, 2, and 3, respectively. ORR and PFS were not significantly different between groups, while prior RS was associated with longer OS (unadjusted HR 0.8, p=0.03). However, after adjustment for Bellmunt score, this association was not significant (table). Upon stratification based on treatment line, OS was longer with prior RS (0.7, p=0.03) for those treated with salvage ICI but this was not significant after adjusting for Bellmunt score. ORR, PFS and OS were not significantly different between pts receiving prior RT only vs RS vs none. **Conclusions:** Prior RS was not significantly associated with longer OS in pts with aUC receiving ICI after adjusting for Bellmunt score. Further work is needed to interrogate tumor-host immune interactions and identify biomarkers that can be prognostic and/or predictive of ICI response. Research Sponsor: None.

	N	ORR % (95% CI)	adjusted OR (95% CI)	N	Median OS, months (95% CI)	adjusted HR for OS (95% CI)	N	Median PFS, months (95% CI)	adjusted HR for PFS (95% CI)
No RS	308	27 (23-33)	Ref.	313	8.8 (6.8-10.9)	Ref.	327	3.7 (3.1-4.6)	Ref.
RS	365	30 (26-35)	1.1 (0.8-1.6)	369	11.3 (8.7-14.3)	0.9 (0.7-1.0)	377	4.5 (3.9-5.6)	0.9 (0.8-1.1)
First-line - no RS	154	34 (27-42)	Ref.	161	10.9 (7.3-13.2)	Ref.	168	3.2 (2.7-3.8)	Ref.
First-line -RS	217	31 (25-38)	0.9 (0.6-1.4)	225	12.4 (8.2-16.5)	0.9 (0.7-1.2)	227	4.7 (3.6-5.9)	1.0 (0.7-1.2)
Salvage - no RS	154	21 (15-28)	Ref	152	7.8 (5.1-9.7)	Ref.	159	5.5 (3.2-6.6)	Ref.
Salvage – RS	148	29 (22-37)	1.4 (0.8-2.4)	144	10.8 (8.4-14.3)	0.8 (0.6-1.0)	150	4.4 (3.4-6.4)	0.8 (0.6-1.0)

Association between sites of metastases (mets) and outcomes with immune checkpoint inhibitor (ICI) therapy for advanced urothelial carcinoma (aUC).

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Background: Different metastatic sites have variable prognostic implications in aUC. However, details on response and outcomes with ICI for particular mets is still unknown. We hypothesized that bone and liver mets would have poor response and outcomes with ICIs. **Methods:** We performed a retrospective cohort study in patients (pts) with aUC who received ICI. We compared overall response rate (ORR) and overall survival (OS) between pts with different mets at ICI initiation. We developed 4 different models: 1) lymph node (LN) only vs other; 2) visceral mets (bone, lung, liver) vs other; 3) bone + liver mets vs bone without liver vs liver without bone vs neither and 4) 6 factor model: a. LN +/- soft tissue/locoregional recurrence b. lung +/- (a) c. bone +/- (b) d. liver +/- (c) e. central nervous system (CNS) +/- (d) and f. other. ORR and OS were compared among groups using multivariable (adjusting for ECOG PS and hemoglobin<10g/dl) logistic regression and cox regression, respectively. **Results:** We identified 984 pts (24 institutions); 703 and 696 were included in OS and ORR analyses, respectively. Median age at ICI start was 71 (range 32-93), 77% white race, 74% men, 67% ever smokers, 72% pure UC, 18% upper tract UC, 55% extirpative surgery. Prevalence of LN, lung, bone and liver mets at ICI start was 74%, 32%, 27% and 21%, respectively. LN-only mets had significantly higher ORR (44% vs 22%, OR 2.6, $p<0.05$) and longer mOS (22 vs 8 months, HR 0.5, $p<0.05$) vs other mets. Visceral mets had significantly lower ORR (21% vs 35%, OR 0.5, $p<0.05$) and shorter mOS (7 vs 17 months, HR 1.8, $p<0.05$) vs non-visceral mets. Pts with bone and liver mets had significantly lower ORR and shorter OS vs those with bone or liver mets, which both had significantly lower ORR and shorter OS vs those with neither and with LN +/- local recurrence (Table). **Conclusions:** In the context of ICI treatment, bone, liver, lung or CNS mets were associated with lower ORR and/or shorter OS, and bone and liver mets were particularly associated with low ORR and short OS. LN-only mets were associated with higher ORR and longer OS. Further work is needed to interrogate site-specific tumor-host immune interactions and identify biomarkers. Research Sponsor: None.

	N	ORR, % (95% CI)	OR (95% CI)	N	mOS, months (95% CI)	HR for OS (95% CI)
No liver/bone	418	33 (29-43)	Ref	418	14 (12-19)	Ref
Bone+/no liver	134	17 (12-25)	0.4 (0.2-0.7)*	136	8 (6-9)	1.6 (1.2-2.1)
Liver+/no bone	91	22 (15-32)	0.6 (0.4-1.1)	98	5 (4-9)	1.8 (1.3-2.4)
Liver+/Bone+	53	9 (4-21)	0.3 (0.1-0.7)*	51	2 (2-5)	2.8 (1.8-4.3)*
a) LN +/- local recurrence	241	37 (31-43)	Ref	240	18 (12-24)	Ref
b) Lung +/- (a)	134	29 (22-37)	0.7 (0.4-1.1)	136	12 (8-19)	1.5 (1.0-2.0)*
c) Bone +/- (b)	133	17 (11-24)	0.3 (0.2-0.6)*	134	8 (6-9)	1.9 (1.4-2.6)*
d) Liver +/- (c)	144	17 (12-24)	0.4 (0.2-0.7)*	148	4 (3-6)	2.4 (1.8-3.2)*
e) CNS+/- (d)	8	25 (6-62)	0.7 (0.1-3.5)	9	6 (0-21)	2.5 (1.3-5.0)*
f) other sites	36	28 (16-44)	0.6 (0.4-1.5)	36	(5-23)	1.2 (0.7-2.1)

*P<0.05

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

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Background: Several PD-1 immune-checkpoint inhibitors including Nivolumab (Nivo) are approved in urothelial cancer. Recently, in the front line setting, improved activity of combined PD-L1 and CTLA4 immune-checkpoint inhibition has been reported and a phase III trial with Nivolumab + Ipilimumab (Nivo+Ipi) is ongoing. Here we report a response-based tailored approach starting treatment with Nivo monotherapy using Nivo+Ipi as immunotherapeutic "boost". **Methods:** Between July 2017 and April 2019 86 patients were enrolled and treated according to protocol version 3 (cohort 1). Patients started with Nivo 240 mg Q2W induction. After 4 dosings and tumor assessment at week 8 (i) responders (PR/CR) to Nivo monotherapy continued with maintenance while (ii) patients with stable (SD) or progressive disease (PD) received 2 cycles Nivo3+Ipi1 followed by another 2 cycles Nivo1+Ipi3 if not responding. Median follow-up is 8.7 months. The primary endpoint is confirmed investigator-assessed objective response rate (ORR) per RECIST1.1. Secondary endpoints include activity of Nivo monotherapy at week 8, remission rate with Nivo+Ipi "boosts", safety, overall survival and quality of life. **Results:** Of the patients 42, 39 and 5 were first, second and third line, respectively. Median age was 67 years (range 45-84), 61 patients (71 %) were male and 25 female. ORR with Nivo monotherapy at first assessment (week 8) was 29 % and 23 % in first and second/third line, respectively. Of the patients 41 received Nivo+Ipi "boosts" after week 8 while 12 received later "boosts". Best overall response (BOR) rate with Nivo induction ± Nivo+Ipi "boosts" was 48 % and 27 % in first and second/third line, respectively. In first line 7/17 (41 %) patients receiving Nivo+Ipi after week 8 had an improved response compared to 2/24 (8.3 %) in second/third line. Of the patients who continued with Nivo maintenance after week 8 and received later "boosts" 2/12 (17 %) had a PR and 2/12 (17 %) improved to SD. Treatment-related AEs will be presented. **Conclusions:** TITAN-TCC explores a response-driven use of Nivo+Ipi as an immunotherapeutic "boost". In first line, this significantly improved ORR compared to the expected response rate of Nivo monotherapy, providing further evidence to the added value of Ipi in combination with Nivo. Further follow-up is ongoing to characterize duration and depth of response. Clinical trial information: NCT03219775. Research Sponsor: Bristol-Myers Squibb.

	First line (n=42)		Second/Third line (n=44)	
n (%)	Nivo mono ORR*	Nivo ± Nivo+Ipi BOR	Nivo mono ORR*	Nivo ± Nivo+Ipi BOR
Complete response	1 (2.4)	3 (7.1)	1 (2.3)	2 (4.5)
Partial response	11 (26.2)	17 (40.5)	9 (20.5)	10 (22.7)
Stable disease	9 (21.4)	4 (9.5)	9 (20.5)	8 (18.2)
Progressive disease	14 (33.3)	10 (23.8)	17 (38.6)	15 (34.1)
Not evaluable/Not assessed**	7 (16.7)	8 (19.0)	8 (18.2)	9 (20.5)

* In first tumor assessment. In first and second line each 1 SD subsequently unconfirmed.
** Includes patients who discontinued/died before disease assessment.

DNA methyltransferase inhibitor guadecitabine combined with cisplatin and gemcitabine chemotherapy (SPIRE): Randomized expansion phase as neoadjuvant therapy for bladder urothelial carcinoma.

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Background: Pre-clinical data support a hypothesis that DNA methyltransferase inhibition will circumvent cisplatin resistance in various cancers including urothelial carcinoma (UC). SPIRE comprised a previously reported phase Ib dose escalation phase for incurable metastatic solid cancers which established a recommended phase II dose (RP2D) for guadecitabine combined with gemcitabine and cisplatin (GC) chemotherapy (Crabb et al, ESMO Congress 2018, abstract 425P). We now report the SPIRE phase IIa randomised dose expansion phase which tested neoadjuvant treatment of bladder UC. **Methods:** Patients had T2-4a N0 M0 bladder UC intended for radical treatment. All patients received an investigator choice of 3 or 4 planned, 21-day, GC cycles (cisplatin 70 mg/m^2, IV, day 8; gemcitabine 1000 mg/m^2, IV, days 8 and 15). 20 patients were randomised (1:1, open label) to whether they also received guadecitabine 20 mg/m^2, SC, on days 1 to 5, and G-CSF prophylaxis 300 μg, SC, on days 15 to 21. The primary objective for the expansion phase was to confirm a safe and biologically effective dose and schedule for this combination for future investigation. Circulating cell free DNA *LINE-1* promotor methylation was measured as a guadecitabine pharmacodynamic endpoint. Trial registration: ISRCTN 16332228. Funding: Cancer Research UK, Astex Pharmaceuticals. Sponsor: University Hospital Southampton NHS Foundation Trust. **Results:** Median age was 68 (interquartile range (IQR) 59-72). 19 (95%) patients were male and 17 (85%) had T2 stage. The commonest grade ≥3 adverse events were neutropenia and thrombocytopenia with one or both affecting 6 (60%) patients in each treatment arm (no grade 5 events). One episode of neutropenic fever occurred (guadecitabine arm). Addition of guadecitabine to GC, versus GC alone, resulted in similar cisplatin dose intensity (median total doses 408 mg (IQR 384-435 mg) and 435 mg (IQR 384-435 mg) respectively) but modestly reduced gemcitabine dose intensity (median total doses 10,450 mg (IQR 9,500-11,400) and 12,768 mg (IQR 9,500-12,768) respectively). All patients completed post-chemotherapy radical treatment (8 cystectomy, 2 radiotherapy, in each arm) with similar timing post chemotherapy and peri-operative morbidity scores. *LINE-1* promotor methylation depletion occurred at cycle day 8 in guadecitabine treated patients. **Conclusions:** Guadecitabine in combination with GC and G-CSF is safe and tolerable in this combination compared to GC alone as neoadjuvant treatment for UC. Radical surgery or radiotherapy delivery, and cisplatin dose intensity, were not compromised. Pharmacodynamic endpoints are optimal with this treatment schedule. Addition of guadecitabine to GC warrants further investigation. Clinical trial information: 16332228. Research Sponsor: Cancer Research UKPharmaceutical/Biotech Company.

Analysis of PFS2 by subsequent therapy in KEYNOTE-361: Pembrolizumab (pembro) plus chemotherapy (chemo) or pembro alone versus chemo as 1L therapy for advanced urothelial carcinoma (UC).

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Background: 1L pembro + chemo did not show statistically superior PFS and OS vs chemo for pts with advanced UC in the phase III KEYNOTE-361 study; OS for pembro vs chemo was not formally tested. We analyzed PFS2 (time from randomization to progressive disease [PD] on first subsequent therapy, or death from any cause, whichever occurs first) by study treatment and subsequent therapy in KEYNOTE-361 (NCT02853305) to determine the effects, if any, of therapy sequence on PFS2. **Methods:** PFS2 was estimated for pts in each treatment arm, who received any subsequent therapy including any anti–PD-(L)1, any therapy other than anti–PD-(L)1, or no therapy. These were exploratory analyses; no formal comparisons were done. **Results:** 1010 pts were randomized: 351 pts to receive pembro + chemo, 307 to pembro, and 352 to chemo. As of Apr 29, 2020, the median (range) time from randomization to data cutoff was 31.7 (22.0-42.3) mo. Subsequent therapy was received by 124/351 (35%), 126/307 (41%), and 215/352 (61%) pts in the pembro + chemo, pembro, and chemo arms, respectively. Subsequent anti–PD-(L)1 therapy was received by 169/352 (48%) pts in the chemo arm vs 23/351 (7%) in the pembro + chemo arm and 14/307 (5%) in the pembro arm. Of pts in the pembro arm who received subsequent therapy, >90% received 2L cisplatin-based or carboplatin-based treatment. Median (m) PFS2 (95% CI) for all pts by treatment arm was 14.1 mo (12.6-16.2) with pembro + chemo, 10.9 mo (9.5-12.9) with pembro, and 10.4 mo (9.8-11.2) with chemo. Across treatment arms, pts in the pembro + chemo arm had the longest mPFS2 with any subsequent therapy (14.5 mo [95% CI 13.1-16.6]) (Table). Pts in the pembro arm who received no subsequent therapy had a longer mPFS2 (12.9 mo [95% CI 8.1-17.9]) vs pts in the chemo arm who received no subsequent therapy (9.4 mo [95% CI 7.6-10.6]). Finally, pts treated with 1L pembro in the trial followed by 2L therapy other than anti−PD-(L)1 had comparable mPFS2 (10.2 mo [95% CI 8.6-12.1]) to pts treated with 1L chemo in the trial followed by 2L anti−PD-(L)1 (11.1 mo [95% CI 10.2-12.9]). **Conclusions:** In this exploratory analysis, treatment sequence of chemo followed by anti−PD-(L)1 upon PD vs anti–PD-(L)1 followed by chemo upon PD did not appear to impact mPFS2. Among pts who did not receive 2L therapy, 1L pembro appeared to be associated with longer mPFS2 than chemo, potentially driven by long-term responders to pembro. Clinical trial information: NCT02853305. Research Sponsor: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	mPFS2, mo (95% CI) by subsequent therapy	
Arm (n/n)	**Anti–PD-(L)1**	**Other than anti–PD-(L)1**
Pembro + Chemo (23/101)	[a]	13.8 (11.8-15.8)
Pembro (14/112)	[b]	10.2 (8.6-12.1)
Chemo (169/46)	11.1 (10.2-12.9)	10.8 (8.3-13.6)

[a] Based on small pt number (n=23); mPFS2 (95% CI) was 17.3 mo (14.8-27.0) [b] Based on small pt number (n=14); mPFS2 (95% CI) was 11.7 mo (9.1-22.3)

449 **Poster Session**

Concomitant antibiotics (ATBs) use and survival outcomes in patients (pts) with muscle-invasive bladder cancer (MIBC) treated with neoadjuvant pembrolizumab (PURE-01 study).

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Background: Administration of single-agent neoadjuvant immunotherapy (IO) proved to be effective and safe in the treatment of MIBC, and the identification of reliable predictors of treatment-failure would allow a more precise implementation in clinical practice. In advanced/metastatic urothelial carcinoma, ATB therapy has a negative impact on IO efficacy by modulating the intestinal microbiota towards a detrimental state of dysbiosis, eventually impairing the host anticancer immunity. However, evidences of such an effect in more confined disease, managed with an intention-to-cure attitude, are still lacking. **Methods:** A post hoc analysis was conducted in pts prospectively enrolled in PURE-01 study (NCT02736266), in which MIBC patients received 3 cycles of neoadjuvant pembrolizumab. ATB use was defined as any ATB administration between 30 days prior to the first pembrolizumab dose and the planned RC. Kruskal-Wallis and Chi-square tests for differences between patients treated or not with ATBs according to baseline characteristics were used. Endpoints of the study were pathologic complete response (ypT0N0) and 12- and 24-mo relapse-free survival (RFS). Multivariable logistic regression (MLR) tested the effect of ATB use on ypT0N0 rate. Secondary, we assessed RFS according to ATB use using Kaplan-Meier and multivariable Cox regression (MCR). Analyses were adjusted for baseline T stage of disease (stage II vs III), PD-L1 expression (CPS >10% vs <10%) and tumor mutational burden (TMB). Sub-analyses explored the effect of different ATB classes on the aforementioned outcomes. **Results:** The study cohort included 149 pts treated with neoadjuvant pembrolizumab, of which 140 (94%) underwent RC. Of all individuals, 48 pts (32%) received concomitant ATB treatment. Median TMB (9.3 Mut/Mb vs 11.4 Mut/Mb, p=0.005) and CPS (9.5% vs. 20%, p=0.04) were lower in the subgroup of patients treated with ATBs. At MLR analysis, ATB use was associated with significantly lower rate of ypT0N0 (OR 0.18, [95%CI] = 0.05-0.48, p=0.001). Patients receiving ATBs exhibited shorter 12-mo (80% [70-93] vs. 95% [91-99]) and 24-mo (63% [48-83] vs. 90% [83-97]) RFS rates than pts non receiving ATB. MCR analyses assessed that ATB treatment conferred higher risk of recurrence (HR =2.64 [1.08-6.50], p=0.03) compared to no ATB treatment, after adjusting for CPS, TMB and clinical stage at diagnosis. Fluoroquinolones were significantly associated with the worst outcomes (12-mo RFS 74% (55-99); 24-mo RFS: 61% (40-91); p=0.011; adjusted HR = 3.28 [1.12-9.60], p=0.03). **Conclusions:** ATB treatment was demonstrated as independently associated with lower rate of ypT0N0 and shorter RFS in MIBC treated with neoadjuvant pembrolizumab. More robust data testing the interactions between immunotherapy and gut and urinary microbiota are urgently needed. Clinical trial information: NCT02736266. Research Sponsor: AIRC Italy.

1L pembrolizumab (pembro) versus chemotherapy (chemo) for choice-of-carboplatin patients with advanced urothelial carcinoma (UC) in KEYNOTE-361.

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Background: 1L pembro is approved in advanced UC for cisplatin-ineligible pts with PD-L1 combined positive score (CPS) ≥10 and any platinum-ineligible pts regardless of CPS in the United States based on single-arm trial data. In the phase III KEYNOTE-361 study, 1L pembro + chemo did not statistically significantly improve PFS or OS vs chemo for pts with advanced UC; formal testing of 1L pembro vs chemo was not performed. We present an exploratory analysis of outcomes with pembro vs chemo for choice-of-carboplatin (carbo) pts in KEYNOTE-361 (NCT02853305). **Methods:** At randomization, choice of platinum agent (cisplatin or carbo) plus gemcitabine for each pt was selected based on investigator's assessment of cisplatin ineligibility. ORR/DOR per RECIST v1.1 by blinded independent central review and OS were determined for all pts selected for carbo ("choice-of-carbo") and also choice-of-carbo pts with CPS ≥10. Risk difference assessment for select AEs for pembro vs chemo was conducted in choice-of-carbo pts who received ≥1 dose study treatment. **Results:** As of Apr 29, 2020, the median (range) time from randomization to data cutoff in the full study cohort was 31.7 (22.0-42.3) mo. At randomization, renal impairment was the most common reason for choice of carbo by investigators (36% of all pts). 170 choice-of-carbo pts were randomized to the pembro arm, and 196 choice-of-carbo pts to the chemo arm. Median OS in this subgroup was 14.6 mo with pembro vs 12.3 mo with chemo (HR 0.83 [95% CI 0.65-1.06]). 18-mo OS rate was 42% with pembro vs 40% with chemo. ORR to pembro vs chemo was 27.6% vs 41.8%. Median (range) DOR with pembro vs chemo was not reached (NR) (3.2+-36.1+ mo) vs 6.3 (1.8+-33.8+) mo. 84/170 (49%) and 89/196 (45%) choice-of-carbo pts in the pembro and chemo arms, respectively, had CPS ≥10. In this subgroup, median OS was 15.6 mo with pembro vs 13.5 mo with chemo (HR 0.82 [95% CI 0.57-1.17]). 18-mo OS rate was 44% with pembro vs 43% with chemo. ORR to pembro vs chemo was 29.8% vs 46.1%. Median (range) DOR with pembro vs chemo was NR (4.2-36.1+ mo) vs 8.3 (2.1+-33.8+) mo. Among treated pts (N=166 for pembro, N=190 for chemo), 112 pts (68%) in the pembro arm and 163 pts (86%) in the chemo arm had grade 3-5 AEs of any cause. Pembro was associated with a higher risk of pruritus, while chemo was associated with a higher risk of decreased white blood cell, neutrophil, and platelet counts, nausea, thrombocytopenia, neutropenia, and anemia. **Conclusions:** Due to the trial design, this subset was not statistically tested and is exploratory. Median OS and 18-mo OS rates did not appear markedly different in the two arms; some parameters such as DOR favored pembro, although longer follow-up is needed to determine median DOR for pembro. The PD-L1 CPS ≥10 did not clearly enrich for responders to pembro in choice-of-carbo pts. Pembro was associated with a lower rate of grade 3-5 AEs of any cause than chemo. Clinical trial information: NCT02853305. Research Sponsor: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

451 **Poster Session**

Pembrolizumab for the treatment of patients with high-risk (HR) non-muscle-invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guérin: Extended follow-up of KEYNOTE-057 cohort A.

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Background: Pembrolizumab (pembro) was approved in January 2020 for treatment of HR NMIBC based on interim results from 96 patients (pts) in the open-label, single-arm, multicenter, phase II KEYNOTE-057 (NCT02625961) study. Here we present updated efficacy and safety results with extended minimum follow-up of 26.3 mo from KEYNOTE-057 cohort A. **Methods:** Pts aged ≥18 years with histologically confirmed Bacillus Calmette-Guérin **(**BCG)–unresponsive HR carcinoma in situ (CIS), with or without papillary tumors, who were ineligible for or declined radical cystectomy (RC) received pembro 200 mg Q3W for up to 24 mo or until disease persistence, recurrence, progression, or unacceptable toxicity. Primary end point: complete response rate (CRR). Key secondary end points: duration of response (DOR) and safety. **Results:** Overall, 101 pts received pembro and 96 were included in the efficacy analysis (5 patients did not meet BCG-unresponsive criteria). Median age was 73 years (range, 44-92), and pts received a median of 12.0 (range, 7.0-45.0) BCG instillations. Median time from enrollment to data cutoff date of May 25, 2020, was 36.4 mo (range, 26.3-48.5). Of 96 pts, CRR was 40.6% (95% CI, 30.7-51.1) at first evaluable disease assessment, and median DOR was 16.2 mo (range, 0.0+ to 36.2). Of 39 responders, 13 (33.3%) remained in CR ≥18 mo and 9 (23.1%) remained in CR ≥24 mo as of the data cutoff date. No pt progressed to MIBC while on study treatment based on protocol-specified disease assessments. CRR was generally consistent with the primary analysis across protocol-prespecified subgroups, including PD-L1 expression status. Forty pts (41.7%) underwent RC after discontinuation of pembro; 35 pts (88%) had no pathologic upstaging to MIBC, 2 (5%) had no available pathology data, and 3 (8%) had evidence of MIBC (all nonresponders); 1 pt had pT2N0 disease at 60 days after the last pembro dose, 1 pt had pT2N1 disease (involvement of a single perivesical lymph node) at 86 days after the last pembro dose, and 1 pt had pT3N1 disease at 457 days after the last pembro dose. For other subsequent treatments, 30 of 96 pts (31.3%) received additional intravesical therapy (eg, BCG), 27 of 96 (28.1%) underwent local procedures (eg, TURBT), and 10 of 96 (10.4%) received systemic therapy. In 101 pts, treatment-related AEs (TRAEs) occurred in 67 pts (66.3%); most frequent were diarrhea, fatigue, and pruritus (10.9% each). Grade 3/4 TRAEs occurred in 13 pts (12.9%). Twenty-two pts (21.8%) experienced immune-related AEs; 3.0% were grade 3-4. Seven pts (6.9%) discontinued due to TRAEs. There were no grade 5 TRAEs. **Conclusions:** With extended follow-up, pembro continued to show durable and clinically meaningful activity in pts who had HR BCG-unresponsive CIS with or without papillary tumors and who were ineligible for or declined RC. No new safety risks were identified. Clinical trial information: NCT02625961. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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A pilot clinical trial of genomic-based therapy assignment with co-expression extrapolation (COXEN) in advanced/metastatic urothelial carcinoma.

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Background: We investigated the Co-eXpression ExtrapolatioN (COXEN) algorithm to select "next best therapy" for patients with advanced/metastatic urothelial cancer based on gene expression profiles. **Methods:** This is a single-arm, open label pilot study, that investigates the COXEN algorithm's ability to use patients' tumor gene expression models to predict sensitivities to 75 FDA-approved anticancer agents. The COXEN results were reviewed and discussed in a multi-disciplinary molecular tumor board. From that a treatment plan was chosen based on monotherapy clinical efficacy data in urothelial carcinoma, combination safety data (combinations of agents were allowed provided phase I data were available), side effect profile/tolerability, response or resistance to prior therapies, therapy contraindications, and feasibility of therapy. The objective of this study was to determine the feasibility of using COXEN as a clinical decision algorithm to make a real-time treatment decision within 21 days of specimen collection in patients with advanced/metastatic urothelial carcinoma. **Results:** A total of 8 patients enrolled and underwent tumor biopsy for COXEN analysis. Five out of 8 patients received COXEN therapy within 21 days of biopsy with various regimens including: vorinostat and etoposide; doxorubicin; sunitinib; doxorubicin and paclitaxel; erlotinib and nab-paclitaxel. There were no objective responses. The 5 patients treated with COXEN therapy had a median potential follow up of 36 months, median overall survival of 8.4 months (95% CI: 5.2 months – not estimable), and median progression free survival of 2.2 months (95% CI: 1.4 – 3.9 months). Grade 3 or 4 adverse events included: febrile neutropenia (n=2), hypophosphatemia (n=1) and hyponatremia (n=1). This trial was terminated early due to a lack of treatment responses. **Conclusions:** The COXEN algorithm is a unique personalized method for selecting therapy for patients with advanced urothelial carcinoma. Although the COXEN method was feasible, it did not demonstrate clinical efficacy in this small cohort of patients. Clinical trial information: NCT02788201. Research Sponsor: U.S. National Institutes of Health.

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Impact of angiotensin blockade on response to PD1/L1 inhibitors for patients with metastatic urothelial carcinoma (mUC).

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Background: The renin-angiotensin system (RAS) is involved in regulation of angiogenesis and cell proliferation. Preclinical data also indicate that angiotensin inhibition may improve drug delivery by enhancing tumor perfusion partly by downregulating transforming growth factor (TGF)-β. Since (TGF)-β appears to be associated with resistance in patients (pts) with metastatic urothelial carcinoma (mUC) receiving PD1/L1 inhibitors, we hypothesized that angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) may enhance the outcomes of mUC pts receiving PD1/L1 inhibitors. **Methods:** Data from mUC pts who received PD1/L1 inhibitors as monotherapy were obtained: pts from the Dana-Farber Cancer Institute (DFCI) served as the discovery dataset, while data from Moffitt Cancer Center (MCC) served as the validation dataset. Data for ACEI and ARB administration was collected with concurrent administration defined as ongoing therapy from the time of starting PD1/L1 inhibitor treatment. A logistic regression was used to investigate the impact of concurrent ACEI/ARB on any regression of tumor (ART, any decrease in size of tumor on scan) as the primary endpoint defined as any tumor regression after controlling for known prognostic factors (performance status, sites of metastasis, neutrophil/lymphocyte ratio, platelet count, hemoglobin). Overall survival (OS), the secondary endpoint, was analyzed using Cox proportional hazards regression. **Results:** Data was available for 178 pts from DFCI (discovery dataset) with mUC who received a PD1/L1 inhibitor of whom 153 (86%) had received prior platinum and 33 pts (18.5%) received concurrent AECI/ARBs. Multivariable analysis controlling for known prognostic factors revealed that patients who received ACEIs or ARBs had greater ART (HR 3.0 [95% CI 1.25-7.17], p = 0.014) and improved OS, (HR 0.49 [95% CI 0.28-0.88] p = 0.016). In the MCC validation dataset, 101 pts were available of whom 59 (58.4%) had received prior platinum and 22 pts (21.8%) received concurrent ACEI/ARBs. Univariate analysis showed that those patients who were treated with ACEI/ARB had an improved ART (OR 3.32 [95% CI 1.22-9.06] p = 0.019). On multivariable analysis, there was a borderline significant association of ACEI/ARB with ART (OR = 3.03, p = 0.075), but no association was observed with OS. **Conclusions:** In this hypothesis-generating study, concurrent angiotensin inhibitors including ACEI or ARBs were associated with tumor regression in mUC pts receiving PD-1/L1 inhibitors. The inconsistent association with OS may be partly due to modest sample size and comorbidities associated with the need for ACEI/ARBs. These results require validation in a prospective study. Research Sponsor: None.

Role of consolidative radiotherapy for metastatic urothelial bladder cancer patients without progression and with no more than five residual metastatic lesions following first line systemic therapy: A retrospective analysis.

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Background: Consolidative local treatment of the primary tumor and metastases in the treatment of metastatic malignancies has shown promising results in several types of primary tumors. The aim of this study is to assess consolidative radiotherapy to the bladder and to residual metastases among metastatic urothelial bladder cancer with no progression following first line systemic therapy, hypothesizing an increase in overall survival and in progression free survival. **Methods:** Between January 2005 and December 2018, patients who received standard first-line chemotherapy for the treatment of metastatic urothelial bladder cancer (mUBC) were retrospectively identified through the database of four Comprehensive Cancer Centers in France. Among them, patients with no disease progression following chemotherapy and with no more than 5 residual metastases were analyzed: patients who received subsequent radiotherapy (of EQD2Gy $>$ 50Gy) to the bladder and residual metastases were included in the consolidative group (RT group), and the other patients were included in the observation group (OBS group). PFS and OS were determined from the start of the first-line chemotherapy using the Kaplan-Meier method. To account for the delay from chemotherapy initiation to consolidative radiotherapy, a Cox model with time-dependant covariates, and a 6-month landmark analyses were performed to examine OS and PFS. **Results:** A total of 91 patients with at least stable disease following chemotherapy and with no more than 5 residual metastases were analyzed: 51 in the RT group and 40 in the OBS group. Metachronous metastatic disease (following definitive treatment of localized UBC) was more frequent in the OBS group (19% vs 5%, p = 0.02); the median number of metastases in the RT group vs in the OBS group was: 2 (1-9) vs 3 (1-5) (p = 0.04) at metastatic presentation, and 1 (0-5) vs 2 (0-5) (p = 0.18) after completion of chemotherapy (residual lesions), respectively. Two grade 3 toxicities (3.9%) and no grade 4 toxicity were reported in the RT group. With a median follow up of 85.9 months (95% IC [36.7; 101.6]), median OS and PFS were 21.7 months (95% IC [17.1; 29.7]) and 11.1 months (95% IC [9.9; 14.1]) for the whole cohort, respectively. In multivariable analysis: consolidative RT in comparison with observation was associated with improved OS in both the standard analysis (HR = 0.47, p = 0.015) and in the 6-month landmark analysis (HR = 0.48, p = 0.026); and with improved PFS only in the standard analysis (HR = 0.49, p = 0.007). **Conclusions:** Consolidative radiotherapy for mUBC patients who have not progressed after chemotherapy and with limited residual disease seems to confer both OS and PFS advantage. Prospective data in that field with addition of avelumab are needed. Research Sponsor: None.

Updated outcomes of POUT: A phase III randomized trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC).

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Background: The POUT trial (CRUK/11/027; NCT01993979) previously reported (with median follow-up 30.3 months) that adjuvant chemotherapy improves disease free survival (DFS) for patients (pts) with histologically confirmed pT2-T4 N0-3 M0 UTUC. Here we present results of a pre-planned analysis updating the primary endpoint and reporting key secondary endpoints including overall survival. **Methods:** 261 pts with UTUC were enrolled following nephro-ureterectomy and randomised (1:1) to 4 cycles of gemcitabine-cisplatin (gemcitabine-carboplatin if GFR 30-49ml/min) or surveillance with subsequent chemotherapy if required. Pts had 6 monthly imaging and cystoscopy for 2 years, then annually to 5 years. Toxicity was assessed by CTCAE v4. Primary endpoint was DFS. Secondary endpoints included metastasis free survival (MFS), overall survival (OS), toxicity and patient reported quality of life (QoL). The trial closed to recruitment early on advice of the independent data monitoring committee due to evidence of efficacy. Time-to-event endpoints are analysed (intention-to-treat) by Cox proportional hazard models. Unadjusted and adjusted (by nodal status, planned chemotherapy type, microscopic margin status, pathological stage) hazard ratios (HR, <1 favouring chemotherapy) are reported. **Results:** From May 2012 to Nov 2017, 261 pts were recruited (129 surveillance; 132 chemotherapy) at 56 UK centres. One participant withdrew consent for data usage and was excluded from analyses. Pts had median age 69 years (range 37-88), 28% pT2, 66% pT3; 91% pN0. To 09/09/2020, median follow up was 48.1 months (IQR: 36.0-60.1). The unadjusted/adjusted HR for DFS was 0.48 (95% CI: 0.33-0.71; p = 0.0003) / 0.50 (95%CI: 0.34-0.75; p = 0.001), and for MFS was 0.52 (95% CI: 0.35-0.77; p = 0.001) / 0.54 (95% CI: 0.36-0.81; p = 0.002). 93/260 (35.8%) pts have died (52/129 [40.3%] surveillance and 41/131 [31.3%] chemotherapy). Chemotherapy conferred a non-statistically significant 28% reduction in relative risk of death (HR = 0.72, 95% CI: 0.47-1.08; p = 0.11; adjusted HR = 0.79, 95% CI: 0.52-1.19; p = 0.26). 3 year OS was surveillance: 67% (95% CI: 58-74%; chemotherapy: 79% (71%-85%). There was no evidence of long-term toxicity associated with chemotherapy (Wilcoxon rank-sum test p-value for worst grade post-6 months = 0.32). Most common grade 2+ adverse events were hypertension (25/240 [10.4%]), lethargy (25/240 [10.4%]) and hearing loss (13/240 [5.4%]). There was no evidence of statistically or clinically relevant differences in QoL. 12 months after treatment (EORTC Q30 global health status mean difference 4.1 and 4.8 at 12 and 24 months respectively in favour of chemotherapy). **Conclusions:** With additional follow-up, the previously reported DFS benefit for chemotherapy was maintained with no detrimental long-term toxicity. No statistically significant improvement in OS was observed. Clinical trial information: NCT01993979. Research Sponsor: Cancer Research UK.

Efficacy of chemohyperthermia (HIVEC) in patients with high-risk nonmuscle invasive bladder cancer (NMIBC) who fail BCG therapy.

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Background: To evaluate Hyperthermic Intra-Vesical Chemotherapy (HIVEC) efficacy regarding 1-year disease-free survival (DFS) rate and bladder preservation rate in patients with high-risk Non-Muscle Invasive Bladder Cancer (NMIBC) who fail BCG therapy or are contraindicated to BCG. **Methods:** Between June 2016 and October 2019, patients treated with HIVEC for high-risk NMIBC who failed BCG (Fail-BCG) or BCG-naive if BCG contraindicated (N-BCG) have been included in our study. These patients had a theoretical indication for cystectomy but were ineligible for surgery or refused it. **Results:** Fifty-three patients, median age 72 [39-93] years, were included (n = 29 Fail-BCG and n = 24 N-BCG). The median follow-up was 18 months. The bladder preservation rate was 92.4%. The RFS rate at 12 months was 60.5%. The RFS rate at 12 months for N-BCG and Fail-BCG groups was respectively 70% and 52.2%. Three patients progressed to muscle-invasive disease, all in the Fail-BCG group and all in the very high-risk EORTC group. Two of them experienced metastatic progression and died from bladder cancer. **Conclusions:** Chemohyperthermia using HIVEC device achieved a RFS rate of 60% at 1 year and enabled a bladder preservation rate of 92%. Given the low risk of progression in the N-BCG group, HIVEC could be a good alternative. Conversely, for patients with very high-risk tumors that fail BCG, cystectomy should remain the standard of care and HIVEC may be discussed cautiously for patients who are not eligible for surgery and well informed of the risk of progression to muscle-invasive disease. Research Sponsor: None.

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TraceIT: A prospective pilot study of a temporary intravesical fiducial marker for bladder cancer radiation therapy.

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Background: Precision image-guided radiotherapy (RT) for patients (pts) with muscle-invasive bladder cancer (MIBC) is limited by daily anatomic variation and difficulty visualizing the tumor bed. We hypothesized that TraceIT, a radiopaque resorbable hydrogel, can be injected around the tumor bed to improve image guidance. We present the results of our pilot trial (NCT03125226) evaluating safety/feasibility of TraceIT in pts undergoing definitive RT. **Methods:** Eligibility included MIBC with plan to receive definitive RT +/- chemo. Fifteen patients were available for analysis (11 enrolled on trial from 2017-2018, plus an additional 4 received TraceIT off study). TraceIT was injected around the circumference of the tumor bed during pre-radiation maximal re-transurethral resection of bladder tumor (TURBT) for all pts, and again during the mid-radiation TURBT to improve visibility in n = 8 pts. The primary endpoint was assessment of interfraction motion on daily cone-beam CT (CBCTs) based on alignment to fiducial vs standard-of-care pelvic bone anatomy. Van Herk (VH) margin equation was used to determine the planning target volume margin optimized for the clinical target volume receiving at least 95%-prescription dose in 90% of pts. Recurrence rates and survival were estimated by Kaplan Meier. Toxicity was measured by CTCAE v4.03. **Results:** Patients underwent RT to a median total dose of 63.5 Gy (range 35.75-66.6), typically to an initial small pelvis field follow by a tumor boost. 14/15 received chemo with RT. Median TraceIT volume was 0.5cc (range 0.3-0.75) per injection site for 4 (range 4-6) sites per patient for total volume of 2cc (range 2-3). All pts demonstrated 100% visibility of TraceIT on initial simulation CT and day 1 CBCT. TraceIT visibility declined slightly over time, with 91.5% of patients having visible TraceIT by the end of the initial RT phase (usually week 5) and 82.5% by end of the boost phase. For the initial phase, alignment to fiducials over bone anatomy allowed for reduced VH margins (0.67cm vs 1.56cm). For the boost phase, the VH margin was similar between fiducial and bone alignment (1.01cm vs 0.96cm). There have been no acute or late complications from TraceIT placement. There were no grade grade (G) 4/5 toxicities; three pts had acute G 3 events, and three pts experienced late G 3 toxicity: two related to hematuria and one from ureteral stenosis. There were no late G≥2 GI toxicities. No patients have undergone cystectomy. At a median follow-up of 22 months, 2-yr OS was 79.1% and 2-yr PFS was 75.4%. **Conclusions:** TraceIT is safe and feasible for use in image-guided RT. TraceIT can increase the precision of RT by facilitating accurate target delineation of the bladder tumor bed and daily motion management which may allow for smaller radiation treatment margins to be used to reduce toxicity and to potentially facilitate safe dose escalation to tumor, which can improve tumor control. Clinical trial information: NCT03125226. Research Sponsor: Augmenix.

Enfortumab vedotin in FGFR3-mutated advanced urothelial carcinoma.

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Background: Enfortumab vedotin (EV) and, for those with FGFR3 mutations (FGFR3+), erdafitinib, are established therapeutic options for refractory advanced urothelial carcinoma. However, optimal sequencing of these agents remains undefined. Here, we report our experience of EV monotherapy with focus on patients (pts) with FGFR3 alterations. **Methods:** Pts who were treated with EV were identified. Clinical data and outcomes were extracted. Tumor genomic profiles by the MSK-IMPACT assay as part of standard of care were reviewed for FGFR3 and other commonly altered gene mutations and tumor mutation burden (TMB). Progression-free (PFS) and overall survival (OS) were measured from start of EV therapy and compared with unadjusted log-rank test. **Results:** 89 patients received EV on completed monotherapy studies (n = 37) or as standard of care. Median age was 62 years (IQR: 62 – 78), 71% were male (n = 63), 28% had liver metastases. Distribution per Bellmunt score (0 – 3) was: 12%, 42%, 37% and 9%. For the entire population, PFS and OS were 5.2 and 11.4 months, respectively, with response rate of 52% among 75 evaluable patients. MSK-IMPACT was available for 80 patients. Overall genomic profile was similar to TCGA cohort except for fewer DNA damage response/repair gene alterations – 15% (ERCC2: 2; ATM: 4, BRCA1: 2, BRCA2: 3, RAD51C: 1) and FGFR3+ rate of 33%. Median TMB was 8.9/Mb (IQR: 5.2 – 13.3). Of the 26 FGFR3+ pts, 8 and 1 received an FGFR3 inhibitor (FGFR3i) before and after EV, respectively. 17 pts have not been exposed to FGFR3i; 13 of whom have progressed on EV and 9 died. Compared to FGFR3- pts, FGFR3+ pts with no prior FGFRi had significantly shorter median PFS on EV (2.5 vs. 6.8 months; HR 0.33 [0.14 – 0.80] $p < .01$) and trend towards shorter median OS (4.9 vs. 14.6 months; HR 0.42 [0.16 – 1.08] $p > .05$). PFS on EV among FGFR3+ pts with prior FGFR3i exposure was 6.7 months, similar to FGFR3- pts (HR 0.77 [0.30 – 1.96] p = .6). Response rates for FGFR3+ with and without prior FGFRi, and FGFR3- pts on EV were 4/7 (50%), 5/13 (38%) and 29/48 (60%). **Conclusions:** In this retrospective study, FGFR+ patients who receive EV first appear to have shorter PFS and lower ORR than those who have received prior FGFRi. Prospective studies on the sequence of EV and FGFR3i in FGFR3+ pts are warranted. Research Sponsor: None.

Efficacy of platinum re-challenge in metastatic urothelial carcinoma (mUC): A retrospective comparison of chemotherapy regimens.

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Background: First-line platinum-based combination chemotherapy (fPBC) is standard of care for fit patients with mUC. Further lines of therapy include immuno-oncology agents, erdafitinib, and enfortumab vedotin, but patients ineligible for these therapies or who subsequently progress may be considered for further chemotherapy. As the choice of chemotherapy regimen is unclear for these patients, we compared the efficacy of subsequent platinum-based chemotherapy (sPBC) and subsequent non-platinum-based chemotherapy (sNPBC) in patients with mUC. **Methods:** Data was analyzed from the Retrospective International Study of Cancers of the Urothelium (RISC), comprising patients from 28 international centers treated 2005-2012. Inclusion criteria were diagnosis of mUC, receipt of fPBC for mUC, and receipt of $\geq$2 cycles of subsequent chemotherapy. Patients who had received prior platinum-based chemotherapy in the non-metastatic setting were excluded. A multivariate Cox proportional hazards model was used to compare overall survival (OS), while χ^2 and student's *t*-test were used for univariate analyses. A two-sided p value of $<$0.05 was considered statistically significant. **Results:** Of 296 patients, 135 received sPBC and 161 received sNPBC. Common sNPBC regimens contained gemcitabine, taxanes, or pemetrexed. Baseline characteristics were similar, including Charlson Comorbidity Index (CCI) and performance status (PS), except more patients in the sPBC group had achieved investigator-designated stable disease or response (SD/R) with fPBC (75.4% vs. 63.3%, p = 0.031) and had higher hemoglobin values (median 11.9 vs. 11.1 g/dL, p = 0.004). OS was superior for patients receiving sPBC (median 7.9 months) compared to sNPBC (median 5.5 months) after adjusting for CCI, PS, presence of liver metastases, time since fPBC, and number of fPBC cycles received (HR 0.72, 95% CI 0.53-0.98, p = 0.035). 70 patients (57.4%) achieved SD/R with sPBC and 65 (44.8%) with sNPBC (p = 0.041). Achieving SD/R with subsequent chemotherapy was not associated with number of fPBC cycles received, but for sPBC was associated with longer time since fPBC (median 5.9 vs. 2.9 months, p = 0.033); the same was not true for sNPBC (median 2.2 vs. 2.6 months, p = 0.057). Achieving SD/R with fPBC was associated with greater likelihood of SD/R with sPBC (63.2% vs. 29.6%, p = 0.002), but not sNPBC (50.5% vs. 38.8%, p = 0.185). Liver metastases were negatively associated with likelihood of SD/R with sPBC (43.8% vs. 63.6%, p = 0.038), but not sNPBC (36.2% vs 49.0%, p = 0.147). **Conclusions:** After treatment with fPBC for mUC, patients able to receive sPBC had better OS compared to those who received sNPBC in a multivariate model. Patients were also more likely to achieve SD/R with sPBC; factors associated with achieving SD/R with sPBC but not sNPBC included longer interim since fPBC, achieving SD/R to fPBC, and absence of liver metastases. Research Sponsor: Fred Hutchinson Cancer Research Center.

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Treatment results from a phase I study of WST11 phototherapy (VTP) for upper tract urothelial carcinoma.

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Background: Localized treatment of upper tract urothelial carcinoma (UTUC) is technically challenging which limits the ability to provide organ-sparing therapies to preserve renal function and representing a serious unmet need. Vascular-targeted photodynamic therapy (VTP) using intravascular photosensitizing agent padeliporfin (WTS11) has demonstrated preclinical safety and effective tumoricidal activity. Endoluminal application of this therapy offers a promising alternative to radical surgery for patients with upper tract cancers seeking to avoid extirpative surgery. Herein we present early results from a phase I dose-finding study of padeliporfin VTP for UTUC. **Methods:** Fourteen patients with recurrent UTUC were treated with up to 2 sessions of endoscopic padeliporfin VTP treatment. Eligibility included residual or recurrent urothelial carcinoma of the ureter or renal pelvis failing prior endoscopic treatment in patients who were unable or unwilling to undergo surgical management by resection of the involved ureter or kidney. WST-11 was administered at 4mg/kg and infused over 10 minutes. An intermedic diode laser was used to illuminate tumors with light at a wavelength 753 nm through a flexible ureteroscope. A light dose escalation model was employed with increasing light fluence from 100mW/cm up to a maximally tolerated dose of 200mW/cm. The primary endpoint was the determination of maximally tolerated laser light fluence rate, with the secondary objective to evaluate treatment efficacy defined by absence of visible tumor and negative urine cytology following treatment. **Results:** Among 14 treated patients, complete response and tumor recurrence rates at 30 days after treatment were 64% and 29%, respectively. A second VTP treatment was performed in 6 (43%) patients. The efficacy rates were comparable among patients who received the intermediate and highest light fluence and between the first and second treatment. At the last follow-up (mean: 11.5 months), 13 patients (93%) had maintained their affected kidney and renal function was not significantly affected. Graded adverse events related to treatment were rigorously evaluated prospectively as the primary endpoint of the trial to be reported separately in detail. Treatment related toxicities were limited, and no ureteral strictures were identified with the procedure. No evidence of increased toxicity was identified among patients who received a second VTP treatment. **Conclusions:** WST11-VTP shows promising evidence of therapeutic treatment effect in low- and high-grade upper tract urothelial tumors with limited treatment related toxicity. These early results provide support for further investigation to evaluate the curative potential for this therapy in a planned multicenter trial. Clinical trial information: NCT03617003. Research Sponsor: Steba Biotech.

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A potential new therapeutic option for the treatment of nonmuscle invasive bladder cancer: Combination of intravesical oncotherad immunotherapy and platelet rich plasma (PRP).

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Background: Effective intravesical therapies remain lacking for non-muscle invasive bladder cancer (NMIBC) when Bacillus Calmette-Guerin fails. OncoTherad is a nanostructured inorganic phosphate complex associated with glycosidic protein, developed by the University of Campinas/ Brazil, which triggers immunomodulatory and antitumor activities. Previous studies have shown that Platelet Rich Plasma (PRP) acts on immune activation and exerts antitumor effects. This study characterized the effects of the OncoTherad associated with PRP in the treatment of NMIBC chemically induced in mice and the modulation promoted in the Toll-like receptors (TLRs) signaling pathway. **Methods:** Forty-two C57BL/6J mice were divided into groups: Control; Cancer (N-ethyl-N-nitrosourea carcinogen, 50 mg/ml); PRP (0.1 ml); OncoTherad (20 mg/ml); OncoTherad+PRP 10 mg/ml and OncoTherad+PRP 20 mg/ml. The intravesical doses (0.1 ml) were instilled once a week for 6 weeks after induction. **Results:** The NMIBC induction decreases ($p<0.05$) body weight, although after treatments the body weight was recovered similarly to the healthy mice. The treatments did not significantly alter the biochemical patterns of the urine and food and water consumption. There was no acute toxicity or kidney damage, and the presence of hydroureter was variable. The urinary bladders of mice treated with Oncotherad associated or not with PRP showed hyperemia associated with the inflammatory condition. The thickening of the urinary bladder wall in the Cancer group was more evident than in the treated groups, in which there were bladders without thickening or macroscopic lesions. Flat carcinoma *in situ* (pTis) was present in 100% of the mice in the Cancer group and the intensity of immunoreactivities for TLR2, IL-6, TLR4, and IRF-3 was significantly weaker in comparison with the Control, indicating suppression of the immune system in the tumor microenvironment. When treated intravesically with PRP only, mice showed 28.6% of tumor progression inhibition rate; with OncoTherad 85.7% and with OncoTherad+PRP 10 mg/ml or 20 mg/ml 71.4%. Intravesical treatments led to distinct activation of TLRs 2 and 4-mediated innate immune system in the interleukins (MyD88-dependent) and interferons (TRIF-dependent) signaling pathways. The combined treatment of OncoTherad+PRP increased ($p<0.05$) the percentage of positive TLR4 urothelial cells and the intensity of immunoreaction for TLR4 compared to the isolated treatments and the immunoreactivities of NF-kB, IL-6, TLR4, IRF-3, and IFN-γ in comparison to the Cancer. **Conclusions:** Intravesical treatment with OncoTherad plus PRP promoted significant inhibition of tumor progression, possibly due to immunomodulatory activity involving the TLR pathway. This association can constitute a therapeutic strategy for refractory NMIBC patients. Research Sponsor: CNPq - National Council for Scientific and Technological Development (Brazil)Other Government Agency.

Modulation of the RANK/RANKL/OPG system and FOXP3+ regulatory T cells in the tumor microenvironment of noninvasive bladder cancer after intravesical oncotherad immunotherapy associated with platelet-rich plasma.

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Background: The activity of the receptor activator of nuclear factor-kβ RANK/RANKL in cancer cells has been correlated with tumor progression and poor prognosis in solid tumors including bladder cancer. Regulatory T cells (Tregs), often identified by FOXP3 biomarker, suppress the anti-tumor response and allow immune tolerance through suppression of T cells. Immunomodulator OncoTherad is an inorganic phosphate nanocomplex associated with glycosidic protein, developed by the University of Campinas/Brazil, with antitumor effects. Previous reports have demonstrated immune activation and antitumor effects of Platelet Rich Plasma (PRP). We evaluated the effects of OncoTherad associated with PRP in the RANK/RANKL system and Tregs in a mouse model of non-muscle invasive bladder cancer (NMIBC). **Methods:** C57BL/6J mice were assigned to groups (n = 42): Control; Cancer (N-ethyl-N-nitrosourea carcinogen, 50 mg/ml); PRP (0.1 ml); OncoTherad (20 mg/ml); OncoTherad+PRP 10 mg/ml and OncoTherad+PRP 20 mg/ml. The intravesical doses (0.1 ml) were instilled once a week for 6 consecutive weeks after induction. **Results:** After NMIBC induction, all animals in the Cancer group showed flat carcinoma *in situ* (pTis) and both percentages of RANK, RANKL, OPG, and FOXP3 positive cells and the intensity of immunoreaction for these antigens were significantly higher in comparison with healthy animals. In addition to ensuring this NMIBC model, these results indicated the involvement of RANK/RANKL in urothelial carcinogenesis and the presence of Tregs in a suppressed immune tumor microenvironment. Mice treated with PRP only showed a 28.6% rate of tumor progression inhibition (TPI) and exhibited papillary urothelial carcinoma (pTa) and pTis. In this group, the intensity of the RANKL and FOXP3 immunoreaction was weaker when compared to the Cancer group. Thus, PRP showed immunomodulatory effects, reducing Tregs that are sources of RANKL. Oncotherad immunotherapy led to an TPI of 85.7%, and benign flat hyperplasia was the most frequent diagnosis. Oncotherad reduced the total RANK and RANKL immunoreactivities and decreased the intensity of RANKL immunostaining in comparison to the Cancer. In the OncoTherad+PRP 10 mg/ml or 20 mg/ml group, TPI was 71.4%, with a predominance of non-malignant lesions such as flat hyperplasia, low-grade intraurothelial neoplasia, and reactive atypia. Treatments with Oncotherad and Oncotherad plus PRP decreased the percentage of FOXP3+ cells and reduced the intensity of FOXP3 immunoreaction compared to the Cancer and PRP groups. **Conclusions:** The tumor inhibition obtained with Oncotherad plus PRP was related to the alteration of the immune profile of the tumor microenvironment by decreasing RANK/RANKL expression and Tregs, resulting in an effective immune response against the tumor. Research Sponsor: CNPq - National Council for Scientific and Technological Development (Brazil)Other Government Agency.

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Heterogeneity in Nectin-4 expression across molecular subtypes of urothelial cancer mediates sensitivity to enfortumab vedotin.

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Background: Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) targeting Nectin-4 (encoded by the *PVRL4/NECTIN4* gene) approved for treatment-refractory metastatic urothelial cancer. Factors that mediate sensitivity or resistance to EV are unknown. In the present study, we sought to 1) examine heterogeneity of *NECTIN4* gene expression across molecular subtypes of bladder cancer and 2) determine if Nectin-4 expression mediates EV sensitivity or resistance. **Methods:** *NECTIN4* expression data from seven muscle-invasive bladder cancer clinical cohorts (n = 1912 total patients) were used to compare relative *NECTIN4* expression across molecular subtypes. The outcome of the gene expression analysis was relative *NECTIN4* expression in the consensus molecular subtypes of bladder cancer. Expression of *NECTIN4* was validated in multiple bladder cancer cell lines. *NECTIN4* was stably over-expressed or knocked down in basal (TCCSUP and UMUC-3) and luminal (HT-1376, HT-1197 and UMUC-9) bladder cancer cell lines, respectively, and EV dose-response assays were performed, as measured by cell proliferation and clonogenic assays. **Results:** *NECTIN4* expression is heterogenous across molecular subtypes of bladder cancer and significantly enriched in luminal subtypes ($p < 0.001$). *NECTIN4* expression is positively correlated with the luminal markers *GATA3*, *FOXA1*, and *PPARG* across cohorts (Spearman's rank correlation $r = 0.57$, $p < 0.0001$ for *GATA3*, $r = 0.37$, $p < 0.0001$ for *FOXA1*, and $r = 0.56$, $p < 0.0001$ for *PPARG*). *NECTIN4* expression is both necessary and sufficient for EV sensitivity in luminal and basal subtypes of urothelial bladder cancer cells. Downregulation of *NECTIN4* led to EV resistance, and EV-resistant cell lines expressed decreased levels of Nectin-4. **Conclusions:** Results of this pre-clinical study suggest that sensitivity to EV is mediated by expression of *NECTIN4*, which is significantly enriched in luminal subtypes of bladder cancer. Downregulation of *NECTIN4* leads to resistance to EV. These findings have implications for biomarker development, patient selection and the inclusion of molecular subtyping in ongoing and future EV clinical trials. Further investigation into Nectin-4 loss as a mechanism of resistance in patients treated on EV is warranted. Research Sponsor: None.

Single-cell DNA targeted sequencing (scDNA-seq) to test therapeutic vulnerabilities in urothelial cancer (UC) patient-derived organoids (PDO).

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Background: Genomic alterations in *FGFR3*, *PIK3CA*, and *CDKN2A* are common actionable targets in urothelial cancer (UC). We aimed to determine the efficacy of alpelisib, a PIK3CA inhibitor, and abemaciclib, a CDK4/6 inhibitor in bladder cancer patient-derived organoid using single-cell targeted DNA sequencing. **Methods:** We established a patient-derived UC organoid (PDO) harboring the *FGFR3* mutation (p.Y375C), the *PIK3CA* (p. E452K) mutation, and *CDKN2A* deletion, which we characterized using whole-genome sequencing. We generated dose-response curves of alpelisib, abemaciclib, and erdafitinib (an *FGFR3* inhibitor) in PDO cells to determine the IC_{50} concentrations. The scDNA-seq (Tapsteri) platform was used to measure changes in the variant allele frequencies (VAF) and clonal fractions post-treatment. The Chi-square test for trend was used to test for linear trend across ordered categories. **Results:** scDNA-seq was performed after treating PDO cells with 3uM erdafitinib or DMSO. A total of 7000 single cells were obtained (4179 cells treated with erdafitinib vs. 2821 cells treated with DMSO). After removing variants mutated in $<$50% of cells, we identified 94 clonal variants. As expected, cells harboring *FGFR3* Y375C have significantly decreased post erdafitinib treatment compared to DMSO-treated cells (66.05% vs. 82.36%, $p<0.0001$). We identified mutations in two genes (*RAB31* and *SMAD4*) that were associated with clonal expansion following FGFR3 inhibition (12% vs. 53% and 13% vs. 26%, respectively). We treated PDO cells with 3uM abemaciclib. We identified three genes harboring SNVs (*RB1*, *GNAQ*, and *SMAD4*). The SNVs harboring cells were significantly decreased after abemaciclib compared to DMSO **(**$p<0.0001$**)**. Then, we treated the cells with 1uM alpelisib for 72 hours alone or combined with abemaciclib (0.1uM). We identified that 100% of cells harbored the *PIK3CA* mutation E452K at pre-treatment, which limited our ability to detect significant changes in VAF post-treatment. Instead, we analyzed the effect on the *FGFR3* Y375C clone. Using trend analysis, there was a significant reduction of FGFR3-mutant cells observed across the three conditions, abemaciclib + alpelisib vs. alpelisib alone vs. DMSO (74% vs. 85% vs. 92%, trend test $p<0.0001$), suggesting *in vitro* efficacy of alpelisib alone and significant synergism with the addition of abemaciclib. **Conclusions:** This study established the feasibility of using scDNA-seq as a promising tool to study the clonal evolution patterns in patient-derived UC organoids. Combined pharmacologic inhibition of CDK4/6 and PIK3CA showed more *in vitro* sensitivity than *PIK3CA* inhibition alone. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

465 **Poster Session**

Characterization of microsatellite instability (dMMR/MSI-H) and mutational landscape in a large contemporary cohort of upper tract urothelial cancer (UTUC) patients.

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Background: UTUC is a rare genitourinary malignancy and a number of studies, limited by small sample sizes, have attempted to characterize its mutational landscape. Because immunotherapy is commonly used for this disease type, we evaluated the prevalence of microsatellite instability and characterized the mutational landscapes of UTUC in a large contemporary patient cohort. **Methods:** UTUC tumor samples were analyzed using next generation sequencing (NGS) (NextSeq, 592 gene panel) or whole exome sequencing (WES) (NovaSeq) (Caris Life Sciences, Phoenix, AZ). Mismatch repair status (deficient [dMMR] or proficient [pMMR]) and microsatellite instability status (MSI-high or stable [MSS]) were detected by immunohistochemistry (IHC), fragment analysis, and NGS. Tumor mutational burden (TMB) was measured by counting all somatic mutations found per tumor (high cutoff $\geq$ 10 mutations per MB). PD-L1 expression was tested by IHC using PD-L1 antibody clones 22c3 (Agilent; positive cutoff CPS $\geq$ 10) and SP142 (Ventana; positive cutoff $\geq$ 5% IC). Pathogenic fusion events were detected using whole transcriptome sequencing (NovaSeq). Statistical significance was determined using the Chi-square test and adjusted for multiple comparison. **Results:** 538 patients with included – median (range) age 71.5 (30-89) years and 37.5% female/62.5% male. Prevalence of dMMR/MSI-H was 3.9% (21/538) and TMB-high was 22.7% (96/423). Significant molecular differences were not detected in primary vs metastatic disease or in male vs female cases. dMMR/MSI-H tumors had higher frequency of TMB-high compared to MSS tumors (100% vs. 19%, p = 0.00003). dMMR/MSI-H tumors also had a higher frequency than MSS tumors for mutations in genes involved in chromatin remodeling (ASXL 82.4%, CREBBP 60%, SMARCA4 40%, KMT2D 95%, ARIDIA 100%, KMT2A 20%, KMT2C 35.3%, NSD1 20%), DNA-damage repair (FANCG 10%, ATM 45%, ATRX 40%) and other biological pathways (RNF43 10%, PTCH1 21.4%, ERBB3 30%, CDKN2A 25%, TSC2 15%, FLNC 15%, HNF1A 20%, CIC 15%, DNMT3A 17.6%); all adjusted $p < 0.05$. Pathogenic fusions were detected in 3.8% (17/443) cases, with FGFR3 fusion being the most common, occurring in 2.7% (12/443) cases. PD-L1 positivity was identified in 33.2% (133/400) cases tested by 22c3 antibody and 28.4% (89/313) cases tested by SP142 antibody. No difference was seen in PD-L1 positivity between MSI-H/dMMR vs. MSS tumors. **Conclusions:** In the largest analysis to date, we found a 3.9% prevalence of dMMR/MSI-high rate in UTUC. All dMMR/MSI-H tumors displayed TMB-high. PD-L1 positivity was comparable between dMMR/MSI-H and MSS tumors. dMMR/MSI-H tumors had a significantly higher rate of mutations in genes involved in chromatin remodeling and DDR biological pathways. These results could inform design of targeted therapy trials in UTUC. Research Sponsor: None.

The prognostic and predictive implications of the 12-chemokine score in muscle invasive bladder cancer.

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Background: Adaptive anti-tumor immunity can be orchestrated by lymph node-like immune cell aggregates within the tumor microenvironment (TME) called tertiary lymphoid structures (TLSs). TLSs are postulated to be the gateway of lymphocyte infiltration into the TME, and are privileged sites for coordinated tumor antigen presentation and lymphocyte priming, differentiation, and proliferation, leading to a robust tumor-specific immune response. A 12-chemokine metagene grouping (12-CK score) has previously been described that correlates with the presence of TLSs in other solid tumor types. In this study, we explored the prognostic implication of the 12-CK score in bladder cancer and its correlation with the presence of TLSs. **Methods:** Cystectomy specimens from 132 patients with bladder cancer were arrayed on Affymetrix microarrays. 12-CK scores were normalized with >1 denoting high scores (12-CK^{Hi}). Immunohistochemistry (IHC) antibody staining was performed for DC-LAMP, CD20, CD4, and CD8. A GU pathologist scored TLSs into Types I-III, with type III representing fully developed TLSs. The Fisher's exact test was used to test the associations between the 12-CK scores and the type of lymphoid aggregate. Overall survival was estimated using the Kaplan Meier method. Findings were validated using 12-CK scores extracted from TCGA transcriptome sequencing data and the IMvigor210CoreBiologies package. **Results:** Twenty-five (n = 25) patients had 12CK scores >1 and were classified as 12CK-High. Pathologic review of 43 bladder tumor specimens confirmed higher levels of Type III TLS patients (33% vs. 9%, p = 0.03), B cells (p = 0.002), CD8 T cells (p = 0.01), and activated DC (p = 0.01) in 12-CK^{Hi} compared to 12-CK^{Lo}. 12-CK^{Hi} was found to have a progression-free survival (PFS, HR 0.29, p = 0.003, Fig1a), disease specific survival (DSS, HR 0.29, p = 0.004, Fig1b), and overall survival (OS, HR 0.55, p = 0.03, fig1c) advantage compared to 12-CK^{Lo} in the Moffitt patient cohort. These results were validated using the publically available RNA expression data from TCGA. TCGA patients with 12-CK^{Hi} (18%,n = 72) had improved PFS (HR 0.55, p = 0.007, fig1d), DSS (HR = 0.40, p = 0.002, fig1e), and OS (HR = 0.59, p = 0.01, fig1f). From the IMVIGOR-210 patient who were 12-CK^{Hi} were more likely to have a complete response ($p < 0.05$, fig1g) and have a 11.2mo OS benefit (fig1h) after treatment using atezolizumab. **Conclusions:** Three important findings emerged from the current study: 12CK-High scores corresponded with formation of TLS in the TME; favorable prognosis in surgically treated MIBC patients; and CR in atezolizumab-treated patients. The findings herein suggest the 12CK gene signature to be a clinically actable biomarker for predicting response to immune checkpoint blockade. We believe the 12CK signature may serve as an important tool to refine patient selection for immune checkpoint blockade treatment. Research Sponsor: None.

Genomic landscape of variant urinary tumor histologies.

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Background: The genetics of urothelial carcinoma (UC), the most common histology of urinary tract (UT) tumors, is well characterized; much less is known about the genomic features of rare histologic variants of UT tumors. We aim to compare the genomic alterations (GA) of UT tumors with adenocarcinoma (AD), small cell (SC), squamous cell (SQ), or plasmacytoid (PC) histologies, to UC tumors. **Methods:** We identified patients with pure variant (AD, SC, SQ, PC) or UC histology with genetic characterization through the GENIE registry. Patient tumor genomic data were captured by Memorial Sloan Kettering Cancer Center (MSK)-IMPACT and Dana-Farber Cancer Institute (DFCI)-Oncopanel NGS initiatives. Tumors with mixed histology were excluded. We limited our analysis to genes tested >1000 times (N=211). Mutation frequencies and copy number variants (CNVs), collectively called GAs, were determined for AD, SC, SQ, PC, and UC, and were compared using the Fisher's Exact test and Kruskall Wallis test. Nominal p values were obtained, and FDR correction was employed ($q < 0.1$). **Results:** We identified 1199 patients with available genomic data who met the inclusion criteria. Histologic distribution was: 32 AD, 13 SC, 15 SQ, 11 PC, and 1128 UC tumors. The median age was 68 years and 77% of patients were male. Statistically significant differences in genetic alterations by subtype are shown in the table below. *ARID1A* and *KDM6A* GAs were higher in UC; PC and SC; *CDH1* GAs higher in PC; *RB1* and *TP53* GAs higher in SC; *SMAD4* GAs higher in AD; and *NFE2L2* GAs higher in SQ. **Conclusions:** Variant UT histologies exhibit a distinct pattern of alterations compared to UC, consistent with their divergent clinical behavior. This suggests different biological origins for these variant histologies and possibly different therapeutic vulnerabilities. Exploring the GAs of these UT tumors in larger datasets is warranted. Research Sponsor: None.

Histologic type	adenocarcinoma (n=32)	plasmacytoid (n=11)	small cell (n=13)	squamous (n=15)	urothelial carcinoma (n=1128)	*q* value
SMAD4	8 (25%)	2 (18%)	0 (0%)	0 (0%)	18 (1.6%)	3.6E-05
RB1	3 (9.4%)	4 (36.4%)	11 (84.6%)	2 (13.3%)	197 (17.5%)	1.1E-04
CDH1	1 (3.1%)	6 (55%)	1 (7.7%)	0 (0%)	30 (2.7%)	1.4E-04
ARID1A	1 (3.1%)	1 (9.1%)	0 (0%)	0 (0%)	291 (25.8%)	0.006
TP53	16 (50%)	7 (63.6%)	12 (92.3%)	9 (60%)	465 (41.2%)	0.02
KDM6A	4 (13%)	0 (0%)	1 (7.7%)	2 (13.3%)	353 (31.3%)	0.07
NFE2L2	0 (0%)	0 (0%)	0 (0%)	4 (26.7%)	23 (2.4%)	0.07

Bladder tumor metabolic alterations in response to IFNα gene therapy.

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Background: Intravesical interferon-alpha (IFNα) gene therapy with Nadofaragene firadenovec has shown clinical efficacy in patients with non-muscle invasive bladder cancer (NMIBC) in a phase III clinical trial, highlighting the therapeutic potential of this approach in a disease with significant unmet clinical need. Optimizing the clinical efficacy of IFNα gene therapy requires an understanding of the underlying therapeutic mechanisms. Here, we investigate the impact of IFNα gene therapy on tumor metabolism using *in vitro* and orthotopic murine preclinical models and clinical trial data to elucidate mechanisms of tumor resistance and identify predictive biomarkers. **Methods:** *In vitro* murine bladder cancer cell lines treated with recombinant IFNα (rIFNα) and lentiviral IFNα (LV-IFNα) were analyzed by whole-transcriptome sequencing, glucose uptake, and lactate production. Preclinical murine bladder cancer models were treated with LV-IFNα (orthotopic tumor model) or Poly(I:C) (flank tumor model), a potent IFN inducer. Disease response was monitored by *in vivo* real-time luciferase imaging. Tumors were harvested and whole-transcriptome sequencing performed to assess effects of IFNα therapy on tumor metabolism and lipidomics. Lipidomic profiling was performed on patient urine samples from a phase II clinical trial of intravesical Nadofaragene firadenovec (7 clinical responders and 6 non-responders) to assess for clinically-relevant differences in lipid metabolism. **Results:** Following IFNα therapy *in vitro* and in murine orthotopic bladder cancer models, we identified downregulation of genes involved in fatty acid synthesis and upregulation of genes involved in glycolysis by whole-transcriptome sequencing. This was confirmed by higher glucose uptake and lactate production by IFNα-treated cells *in vitro*. These findings were recapitulated in whole-transcriptome sequencing data of human bladder tumors treated with intravesical Nadofaragene firadenovec. Lipidomics performed on murine MB49 tumors treated with poly(I:C) identified 79 upregulated lipids, including phosphotidyl choline, spingomyelin and phosphatidyl ethanolamine, and 12 downregulated lipids, notably the cardiolipin class. Lipidomics performed on patient urine samples collected pre- and post-treatment with intravesical Nadofaragene firadenovec detected >592 lipids with distinct expression profiles differentiating clinical responders and non-responders at both timepoints. **Conclusions:** We describe novel modulation of glucose and lipid metabolism by bladder tumor cells in response to IFNα gene therapy. These metabolic changes were reproducible across *in vitro*, *in vivo* and clinical trial studies and improve our mechanistic understanding of IFNα gene therapy, identify tumor escape pathways targetable with combination therapy regimens, and identify a new class of biomarkers for predicting clinical response of NMIBC to IFNα gene therapy. Research Sponsor: None.

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Hyperthermia, bladder pressure, and intravesical drug delivery.

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Background: Little is known about the pharmacokinetics of intravesical chemotherapies. Various parameters can be altered including temperature, dwell time, drug concentration, and bladder pressure. Here, we hypothesize that increasing bladder pressure during instillation will improve drug delivery. **Methods:** An ex-vivo porcine model was developed to evaluate determinants of drug penetration into the bladder wall. Porcine bladders were suspended in isotonic saline at 37°C with a three-way Foley catheter in the bladder. Temperature probes were positioned in the extravesical bathing solution, bladder lumen, and sutured to the detrusor to ensure maintenance of desired temperatures. 2g gemcitabine in 100mL normal saline was heated to 43°C and circulated through the bladder using the Combat Bladder Recirculation System. Bladder pressures were monitored throughout each trial. After 60 minutes of dwell time, rapid dissection was performed to obtain full-thickness bladder samples from the bladder dome, posterior wall, trigone, and left and right lateral walls. Tissue was homogenized and liquid chromatography with tandem mass spectrometry (LC/MS/MS) was performed to measure gemcitabine concentration within the bladder wall. Linear regression and Pearson correlation were performed to determine the association between mean bladder pressure during instillation and drug concentration within the bladder wall. Multiple linear regression was conducted to control for bladder location and thickness. **Results:** Gemcitabine concentration within the bladder wall was measured 25 times across five trials. Mean gemcitabine concentration within bladder wall was 3.68 mg/g (sd 1.35). Pressure ranged from 149.8 mmHg to 277.7 mmHg (mean 194.8, sd 22.0). On univariate analysis, higher pressure was associated with increased gemcitabine concentration within the bladder wall (correlation = 0.49, p = 0.013). This result persisted after adjusting for bladder location (β = 0.49, p = 0.006) and thickness (β = 0.70, p = 0.03). Unstandardized regression coefficient in each of the models was 0.099 (mmHg x g)/mg, demonstrating that for each pressure increase of 10mmHg there was an associated increase in gemcitabine concentration of approximately 1 mg/g (Table). **Conclusions:** Data suggest that bladder pressure dramatically improves the extent of gemcitabine penetration into the bladder wall. Future research is needed to evaluate the therapeutic effect of increased gemcitabine delivery to target tissue in patients with bladder cancer. Research Sponsor: Urology Care Foundation Residency Research Award from American Urological Association, Pharmaceutical/Biotech Company.

Predicted gemcitabine concentrations within the lateral bladder wall at different pressures as predicted by regression model.

Bladder Pressure mmHg	Predicted Gemcitabine Concentration mg/g (95% CI)
170	1.58 (-0.3 - 3.48)
180	2.58 (1.30 - 3.85)
190	3.57 (2.77 - 4.37)
200	4.56 (3.76 - 5.37)
210	5.55 (4.28 - 6.83)
220	6.55 (4.65 - 8.45)
230	7.54 (4.98 - 10.10)
240	8.54 (5.29 - 11.78)
250	9.53 (5.60 - 13.46)
260	10.52 (5.90 - 15.14)

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Genomic characterization of bladder cancer with variant histology.

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Background: Up to 25% of tumors are of pure variant or mixed urothelial and variant histology. The presence of variant histology may be associated with more advanced stage at presentation and a poorer response to systemic therapy. While histomorphologic assessment provides important prognostic information, genomic analysis of tumors can provide important insight into the biology of disease and inform treatment. In this analysis we performed genomic sequencing of tumors from patients with bladder cancer with variant histology. **Methods:** Our prospectively generated institutional cohort of molecularly profiled bladder and upper tract tumors contains over 2,000 samples including nearly 300 primary bladder tumor samples from patients with variant histology. Targeted sequencing with MSK-IMPACT was used to identify alterations in cancer-associated genes and to describe trends across variant subtypes. To explore and compare tumor and immune cell heterogeneity, single-cell RNA sequencing (scRNA-seq) was performed on a subset of specimens. **Results:** Our cohort included patients with pure urothelial carcinoma not otherwise specified (NOS), as well as squamous, small cell, pure adenocarcinoma and urothelial carcinoma with glandular differentiation, micropapillary, nested, and plasmacytoid variants. Compared with urothelial carcinoma NOS, nearly all small cell tumors had mutations in *TP53, RB1,* and *TERT*. Squamous tumors had similar mutational frequencies as urothelial carcinoma NOS. Pure adenocarcinoma had frequent mutations in *TP53*, *KRAS*, and *PIK3CA*, resembling colorectal adenocarcinomas, while urothelial carcinoma with glandular differentiation resembled NOS. Micropapillary variant commonly had *ERBB2* amplifications. Nested variant was more commonly found to have *RHOA* mutations and *FOXA1* amplifications. Finally, nearly all plasmacytoid variants had pathognomonic alterations in *CDH1*. To further explore heterogeneity in tumor and immune cell populations, scRNA-seq was performed on four samples from patients with urothelial carcinoma NOS, squamous, micropapillary, and nested variants, showing distinct tumor cell clusters and varying contributions of immune cells from each variant. **Conclusions:** While the distribution of oncogenic mutations differed among distinct histologic variants, a pathognomonic DNA alteration was not found for most variant histologic subtypes. Within the context of a larger effort to characterize bladder cancer with variant histology, scRNA-seq may reveal differences in immune cell population infiltrates. Further efforts will aim to characterize these cohorts with whole exome sequencing and mutational signatures, and increase the number of samples per histology and representation of variant histologies for scRNA-seq. Research Sponsor: U.S. National Institutes of Health.

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Molecular subtype variation within metastasis of urothelial carcinoma.

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Background: Molecular subtyping of cancer based on gene expression is a new prognostic tool with potential to guide treatment in the future. Urothelial carcinoma is one such cancer for which numerous molecular subtyping systems have been developed, but the diversity of these systems has hindered their clinical application. Recently, a consensus classification system was derived from six independent systems, defining six molecular classes with distinct oncogenic mechanisms and mutations (Kamoun A, et al. 2020). Considering the high heterogeneity in urothelial carcinoma, we hypothesized that molecular subtype variation may occur between primary and metastatic samples. We further evaluated whether variation in subtype was associated with any unique patient characteristics. **Methods:** As part of the University of Washington Bladder Cancer Rapid Autopsy Program (BCRAP), primary and metastatic tumor tissue samples were acquired from 14 deceased patients with urothelial carcinoma within 6 hours of death. Patient history was collected and deidentified for analysis. RNA exome sequencing was used for assigning molecular subtype for each of the 61 tumor samples, using the consensus and six comprising systems. **Results:** Molecular subtype variation within metastatic tumors according to any classification system was detected in 8 out of 14 patients, independent of histologic morphologies. Amongst the patients with variation, on average 2.1 out of 7 classification systems identified a major difference in subtype between sites. Patients with variation (mean age 70 years (SD 7 years)) were older than those without variation (mean age 59 years (SD 11 years), P = 0.04). Furthermore, patients with variation tended to have decreased survival from diagnosis and received less chemotherapy, although these were not statistically significant ($p > 0.05$). **Conclusions:** Molecular subtype variation within metastasis is relatively common amongst BCRAP patients with urothelial carcinoma. Older patients are more likely to have variation, possibly due to a higher tumor mutation burden. Potential variation must be taken into account when considering prognosis and developing a recommended drug regimen specific to molecular subtypes. Research Sponsor: None.

Impact of *FGFR2/3* activating genomic alterations on response to enfortumab vedotin in metastatic urothelial carcinoma (mUC).

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Background: Enfortumab Vedotin (EV), an antibody-drug conjugate that targets nectin-4, is approved for metastatic urothelial carcinoma (mUC) progressing post-platinum and PD1/L1 inhibitor therapy. Erdafitinib is approved in patients for post-platinum mUC with activating genomic alterations in *FGFR2/*3, but the activity of EV in this subset is unclear. We investigated the activity of EV in patients (pts) with mUC based on *FGFR2/*3 genotype to inform management. **Methods:** In this multi-center, retrospective analysis, we assessed the objective response rate (ORR) to EV in mUC pts with and without *FGFR2/3* genomic alterations detected by targeted panel next-generation sequencing. Activating gene fusions and known hotspots mutations in the two genes were considered. Descriptive analysis of ORR and patient characteristics was performed. Fisher's exact test and binomial test with two-tailed *p*-value were used. **Results:** 40 pts were available from 4 institutions. Most pts were male (31/40, 78%) and the median age at start of EV was 74.1 (range 49 – 90) years. Ten patients (25%) had upper tract urothelial carcinoma (UTUC), and 33 (82%) had baseline ECOG performance status of 0-1. 31 of 39 patients had received both platinum-based chemotherapy and PD1/L1 inhibitors. Seven patients had confirmed activating hotspot *FGFR3* mutations (p.S249C or p.Y373C). One pt had *FGFR2* high-level amplification (HA), and one had *FGFR3* HA. Of 36 patients evaluable for ORR, 18 had partial response (PR), 12 had stable disease (SD) and 6 had progressive disease (PD). Patients with *FGFR2/3* activating mutations exhibited an ORR that was not statistically different compared to patients without no mutations: 2/7 (29%; 90% CI: 5 – 66%) vs. 16/29 (55%; 90% CI: 38 – 71%) respectively (*p*-value = 0.4). 3/7 patients with *FGFR3* hotspot mutations received an FGFR2/3 inhibitor and none responded; one of them had a sequential response to EV. **Conclusions:** In this multi-center retrospective cohort, *FGFR2/3* activating genomic alterations did not appear to compromise response to EV in mUC. Larger studies are required to confirm our findings and optimal sequencing of EV and erdafitinib in mUC pts with FGFR2/3 genomic alterations requires further assessment. Research Sponsor: None.

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Prognostic impact of serum cytokeratin 19 fragments in patient with metastatic urothelial cancer (mUC) treated with first-line chemotherapy.

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Background: Even today, when several immune checkpoint Inhibitors have been approved for the treatment of metastatic urothelial cancer (mUC), cytotoxic chemotherapy (CTC) still remains the mainstay for first-line treatment. We believe that the prognostic factors for the first-line CTC have become more important again and need to be re-analyzed. Current guidelines do not yet provide recommendations for any serum tumor markers in patients with mUC. Previous studies have shown that serum cytokeratin 19 fragments levels (sCK) were correlated with depth of tumor invasion and metastatic burden in patients with bladder cancer. In this study we evaluated whether sCK, and other clinical parameters could predict overall survival (OS) in patients with mUC treated with CTC. **Methods:** Two hundreds fifty two patients with mUC received CTC from December 2006 to 2016 at our institution. sCK had been measured in 128 patients at diagnosis of mUC. OS rate were analyzed by Kaplan–Meier curves and log-rank test. Multivariate analysis was carried out using the Cox hazards model. Tumor burden (TB) was measured based on Response Evaluation Criteria In Solid Tumor (version 1.1). **Results:** Of 128 patients, with median age of 72 (44-93), 36 (28%) had lung metastasis, 11 (9%) had bone metastasis, 10 (8%) had liver metastasis (LM). Ninety five (74%) patients received platinum based chemotherapy as a first-line treatment. During the median follow-up period of 19 (1-89) months, 72 patients (70%) had died. A 1-year (1y) OS was 51% and a 2y-OS was 36%. On univariate analysis, performance status (PS) (HR2.0, $p<0.005$), sCK (HR3.9, $p<0.001$), CRP (HR4.0, $p<0.001$), neutrophil-lymphocyte ratio (HR1.9, $p<0.049$), LM (HR2.0, $p=0.042$) and TB (HR2.4, $p<0.001$) were the significant prognostic factors for OS. On multivariate analysis, PS (HR2.0, 95%CI (1.05-3.85) p=0.036), sCK (HR3.1, 95%CI (1.3-8.3), p=0.011), and LM (HR3.0, 95%CI (1.06-6.98), p=0.022) were the independent prognostic factors for OS. Based on these 3 factors we divided patients into three groups, good risk (G, 0 factor), intermediate risk (I, 1 factor) and poor risk (P, 2-3 factors). There was a significant difference between the three groups. (G vs I: $p<0.001$, I vs P: p=0.001). **Conclusions:** PS, sCK, and LM were the independent prognostic factors for OS in patients with mUC receiving CTC. For the patients in good or intermediate risk with this score, early exposure of ICIs should be performed after CTCs. Treatment strategy should be changed in patients with poor risk since CTC is primary refractory in such population. Research Sponsor: None.

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High-throughput global transcriptional profiling to identify the STAT3 signaling pathway as a potential biomarker for immune checkpoint inhibitor resistance in metastatic/advanced urothelial carcinoma.

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Background: Advanced/metastatic urothelial carcinoma (UC) is a significant public health burden with median overall survival of 15 months. Although, immune checkpoint inhibitors (ICI) have provided an additional second line treatment option, only 15-40% of patients will respond. There has been much effort in determining the mechanisms of immunotherapy resistance and predictive biomarkers to further improve these treatments. **Methods:** Pre-treatment genomic sequencing data derived from FFPE samples from the IMVIGOR210 clinical trial (n=298) was accessed for analysis. Briefly it was a single arm phase II clinical trial where advanced/metastatic UC patients refractory to platinum chemotherapy treatment received the ICI atezolizumab. This study has been published with detailed methods (PMID: 28950298). The raw sequencing data was pre-processed using standard QC measures and aligned to the human reference genome (hg38). The resulting outputs were then normalized and processed to generate the gene level counts for differential gene expression (DGE). We did DGE analysis comparing patients who had clinical benefit (CR, PR, SD) vs non-clinical benefit (ie. PD) to atezolizumab. The list of differentially expressed genes were then analyzed using various gene ontology, pathway and systems biology tools (IPA, Enrichr, and X2Kweb). Further subset analysis was done using gene-gene correlations (ie. PD-L1 and STAT3) and clinicopathologic features (eg. gender, race, smoking history). **Results:** Among the 298 patients in this study, there were 25 with CR, 43 with PR, 63 with SD, and 167 with PD based on clinical response to atezolizumab. Subgroup analysis for CR vs PD patients found that approximately 847 genes were differentially expressed with statistical significance ($p \leq 0.05$). IPA analysis for this list of differentially expressed genes found among the top signaling pathways were "primary immunodeficiency" and "sirtuin signaling". Further subset analysis of 39 genes ($p \leq 0.01$) enriched in PD patients using Enrichr and X2kweb found that there was an overrepresentation of STAT3 signaling genes (hypergeometric p-val $6.32x10^{4}$). **Conclusions:** Our results found that when the transcriptional profiles of CR vs PD there was differential gene expression in STAT3, primary immunodeficiency, and sirtuin signaling pathways. Of note it has been reported that STAT3 signaling can modulate immune activity and its expression is correlated with poor prognosis in urothelial carcinoma patients. These results warrant a larger study to see if STAT3 signaling is a potential biomarker for ICI resistance. If validated this may indicate that the STAT3 pathway is a potential therapeutic target to overcome ICI resistance and improve the efficacy of these agents. Research Sponsor: American Cancer Society Intramural Pilot Grant.

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CDKN2A alterations as markers of immune checkpoint blockade (ICB) resistance in urothelial carcinoma (UC).

Amin Nassar, Elio Adib, Elie W. Akl, Sarah Abou Alaiwi, Pier Vitale Nuzzo, Tarek H. Mouhieddine, Guru Sonpavde, Robert I. Haddad, Marios Giannakis, F. Stephen Hodi, Toni K. Choueiri, David J. Kwiatkowski; Brigham and Women's Hospital, Boston, MA; Dana Farber Cancer Institute, Boston, MA; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA; Dana Farber Cancer Institute/Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: ICB has shown clinical benefit across several metastatic carcinomas; however, predictive biomarkers are still lacking. *CDKN2A* is one of the most commonly altered genes across human cancers. With prior studies giving conflicting evidence regarding the association between *CDKN2A* alterations and ICBs, we examined the impact of *CDKN2A* alterations on clinical outcomes in UC patients treated with ICBs. **Methods:** Of 809 patients at the Dana Farber Cancer institute (DFCI) treated with ICBs only and with relevant cancer types and targeted exome sequencing data (Oncopanel), 235 (29%) had loss-of-function (LOF) mutations or homozygous deletions in *CDKN2A*. Overall survival (OS) was compared by Cox logistic regression between *CDKN2A* altered and *CDKN2A* wild type (WT) patients. Hazard ratio (HR) was derived using multivariable analysis (MVA), adjusted for prior lines of therapy and tumor mutational burden (TMB). A validation cohort from Memorial Sloan Kettering Cancer Center (MSKCC) (Samstein et al., *Nature Genetics*, 2019) of 811 cancer patients treated with ICBs was analyzed in a similar manner, adjusted for TMB. As a control, the association between *CDKN2A* alterations and OS was examined in a cohort of platinum-treated UC patients (N = 56) to determine whether *CDKN2A* alterations were predictive of response to ICIs. **Results:** For the DFCI and MSKCC cohorts, median follow-up was 26.9 and 24 months (m), respectively. In the DFCI and MSKCC cohorts, *CDKN2A* alterations were found in 32/90 (35%) and 22/104 (21.2%) of UC, respectively; 4/55 (7.3%) and 3/131 (2.3%) of renal cell carcinoma, respectively; 73/178 (41%) and 45/194 (23.2%) of melanoma tumors, respectively; 86/370 (23.2%) and 26/260 (10%) of non-small cell lung cancer (NSCLC) tumors, respectively; 18/66 (27.2%) and 4/53 (7.5%) of esophagogastric tumors, respectively; and 22/50 (44%) and 11/69 (15.9%) of head and neck, respectively. *CDKN2A* alterations were significantly associated with shorter OS and TTF in the DFCI UC and melanoma cohorts by MVA, and showed a trend towards significance in the MSKCC UC cohort (Table). There was no significant association between *CDKN2A* alterations and OS for the other cancer types in both cohorts; and no association with OS or TTF was seen in the DFCI cisplatin-treated UC cohort. **Conclusions:** *CDKN2A* alteration status may serve as a predictive biomarker in patients with UC treated with ICBs. Further studies are needed to examine the mechanism of this clinical effect. Research Sponsor: None.

UC cohort	*CDKN2A*-altered	*CDKN2A* WT	MVA (adjusted HR)
DFCI (N = 90): Median OS (51/90 events)	13.9m (6.2–19.8)	32.1m (15.1–NR)	2.1 (1.2–3.7)
DFCI: Median TTF (67/90 events)	4m (2.6–7.0)	10.4m (5.6–32)	2.1 (1.3–3.5)
MSKCC (N = 104): Median OS (59/104 events)	9m (6–19)	15m (10–NR)	1.5 (0.9–2.8)

TERT promoter mutation as a prognostic marker in patients with advanced urothelial carcinoma treated with immune checkpoint inhibitors.

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Background: Reliable predictive markers are lacking in patients (pts) with locally advanced or metastatic urothelial carcinoma (aUC) treated with immune checkpoint inhibitors (ICI). We sought to determine whether specific genomic alterations could be used to predict overall survival (OS) in this patient population. **Methods:** We undertook a retrospective cohort study of pts with aUC who received ICI and underwent genomic profiling by next-generation sequencing (NGS). All patients underwent NGS using commercially available platforms (e.g. Foundation Medicine, Strata, Invitae), or testing on the CLIA-certified institutional panel UCSF500. Associations between the 20 most frequently altered genes and OS were first examined by Cox regression. Genes with a $p < 0.1$ on univariate analysis and relevant clinical variables were then included in a multivariable analysis. **Results:** We identified 78 pts treated with ICI for aUC with available genomic profiling results. Median age at ICI initiation was 71; the majority of patients had visceral metastases (70.5%), ECOG performance status ≤1 (62.8%) and received ICI in the post-platinum setting (52.6%). Objective response rate in this cohort was 35.9%, median progression free survival was 4.0 months (95% CI 2.6-10.5) and median OS was 17.5 months (95% CI 14.1-NR) from ICI start. The most commonly altered genes were the TERT promoter (TERTp) (61%), TP53 (52%), RB1 (31%), CDKN2A(29%) and CDKN2B (27%). On univariable analysis there was a trend towards longer OS in pts with TERTp mutations (HR 0.53, 95% CI 0.27-1.06, p = 0.07), and shorter OS in pts with CDKN2B mutations (HR 1.91, 95% CI 0.98-3.73, p = 0.06). Both mutations were included in a multivariable analysis. After adjusting for known prognostic variables (ECOG PS, visceral metastases, albumin, hemoglobin, body mass index [BMI], neutrophil to lymphocyte ratio [NLR], and histology), the presence of a TERTp mutation was significantly associated with improved OS (HR 0.30, 95% CI 0.10-0.93, p = 0.04; Table). **Conclusions:** The presence of a TERTp mutation was an independent predictor of improved OS in a cohort of aUC pts treated with ICI. Other common mutations and clinical variables were not associated with OS on a multivariable analysis. These findings are hypothesis-generating and prospective validation is needed. Research Sponsor: None.

Multivariable analysis of OS including known prognostic variables and mutations with p<0.1 on univariable analysis.

Characteristics	HR (95% CI)	p
TERTp mutation	0.30 (0.10-0.93)	0.04
CDKN2B mutation	1.86 (0.55-6.26)	0.32
ECOG PS ≤1 vs ≥2	0.38 (0.11-1.32)	0.13
Presence of visceral metastases	2.47 (0.73-8.33)	0.14
Albumin	0.49 (0.18-1.32)	0.16
Hemoglobin ≥10 vs <10 g/dL	0.41 (0.1-1.75)	0.23
BMI	0.93 (0.84-1.02)	0.14
NLR <5 vs. ≥5	1.83 (0.50-6.74)	0.36
Pure UC vs mixed or pure variant histology	1.09 (0.32-3.74)	0.89

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Plasmacytoid urothelial carcinoma (UC) are luminal tumors with similar immune microenvironment as compared to conventional UC.

Myriam Kossai, Camélia Radulescu, Julien Adam, Anaïs Dziegielewski, Nicolas Signolle, Mathilde Sibony, Thierry Lebret, Yves Allory, Mathieu Rouanne; Centre Jean Perrin, Clermont-Ferrand, France; Hôpital Foch, Suresnes, France; Hôpital Paris Saint-Joseph, Paris, France; Gustave Roussy Institute, Villejuif, France; Hôpital Cochin, Paris, France; Université d'Angers, Angers, France; Institut Curie, St-Cloud, France

Background: Plasmacytoid urothelial carcinoma (UC) is a rare pathological variant of UC with low chemotherapeutic sensitivity and dismal outcomes. The molecular and immune profiles of such tumors remain poorly investigated. Herein, we investigated the phenotypical features of a cohort of plasmacytoid UC (n = 32) by comparison to a control group of conventional high-grade UC with matched clinicopathological characteristics (n = 30). **Methods:** Histopathological analysis included the following antibodies: p63, GATA3, CK5/6, CK20 and HER2. In addition, the density of intra-tumor $CD8^+$ lymphocytes, and PD-L1 expression in tumor (TC) and immune cells (IC) were evaluated. Clinical data were collected. **Results:** Plasmacytoid UC expressed GATA3 (97% vs 86% p = 0.18), CK20 (59% vs 36% p = 0.08) markers and showed a significantly higher rate of HER2 overexpression (2+ and 3+ score: 25% vs 0%, $p < 0.01$) compared to controls. A significantly lower expression of CK5/6 (22% vs 56%, $p < 0.05$) and p63 (41% vs 80%, $p < 0.05$) was observed in plasmacytoid UC compared to controls. The density of tumor-infiltrating CD8+ cells was similar between plasmacytoid and conventional UC (p = 0.5). PD-L1 expression on IC was similar compared to conventional UC (p = 0.3). Overall survival at 5 years was significantly lower among patients with plasmacytoid UC compared to patients with conventional UC (p = 0.02). **Conclusions:** Together, our study demonstrated that plasmacytoid UC belong to the luminal subtype and display a rather inflamed microenvironment similar to conventional UC. These data support the inclusion of plasmacytoid variant of UC in clinical trials evaluating immune checkpoint inhibitors monotherapy or combination immunotherapeutic strategies. Research Sponsor: None.

RNA-seq analysis of non-muscular invasive bladder cancer to reveal different gene expression profiles between smoking and non-smoking patients.

Zhichao Fu, Shenghua Liu, Jianfei Wang, Ning He, Yadong Yang, Tianyuan Xu, Shrestha Anil, Yang Yan, Cheng Li, Zongtai Zheng, Xin Li, Xudong Yao; GloriousMed Clinical Laboratory (Shanghai) Co., Ltd., Shanghai, China; Department of Urology, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China; National Academy of Medical Sciences, Bir Hospital, Nepal, Shanghai, Nepal; Department of Urology, Taizhou Central Hospital, Taizhou, China; Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China

Background: Bladder cancer is the ninth most common malignancy in the world, approximately 75% of patients are diagnosed with non-muscle invasive bladder cancer (NMIBC). Smoking has been established to be a carcinogenic risk factor of bladder cancer. Nevertheless, the detailed relationship between smoking and progression of NMIBC are poorly understood. In this study, we revealed high expressed genes in smoking patients were significantly related to tumor progression in NMIBC patients. **Methods:** A total of 54 NMIBC patients including 19 never smokers and 35 smokers (current smokers and previous smokers) were enrolled in this study.The gene expression profiles were obtained by RNA-seq and the differentially expressed genes between smoking and non-smoking patients were identified using DESeq2 .The further analysis of the association between genes expression and patient survival in NMIBC cohorts(Jakob et al., 2016)and IMvigor 210 cohorts(Jonathan et al., 2016)by Kaplan-Meier survival estimate. **Results:** We identified 46 differentially expressed genes ($p<0.05$) in smoking and non-somking NMIBC patients. IDO1 and KRT14 gene, which related to bladder cancer progression and poor prognosis, was identified significantly higher expressed in somking group compared with non-smoking and they have a logFC of 2.6,3.9 with FDR 1.83E-5,3.40E-5 respectively. The expression of other genes, including *KRT6A*,*CASP14*, *SERPINA1*, *MYO3A* and *IL2ORB*, were significantly higher in smoking patients compared to non-somking. Notably, survival data analysis from 476 NMIBC cohorts showed that *IL2ORB* had a significant relationship with poor PFS($p = 0.021$) and in the Mvigor 210 Cohort including 310 advanced or metastatic urothelial carcinoma patients treated with atezolizumab, we found that the high expression of *IL2ORB* was significantly related to poor OS($p = 0.002$). **Conclusions:** We identified 14 genes related to tumor progression were significantly higher in smoking NMIBC patients than in non-smoking. Among these genes, the expression of *IL2ORB* was related to the poor prognosis of NMIBC, and it may correlates with reduced clinical benefit of immunotherapeutic in patients with urothelial carcinoma. Research Sponsor: None.

Comprehensive genomic profiling (CGP) to reveal new opportunities and challenges in muscle-invasive bladder cancer (MIBC).

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Background: MIBC is an aggressive disease and a limited number of patients (pts) will benefit from neoadjuvant chemotherapy (NAC) or immunotherapy. CGP may help identify prognostic factors, predictive biomarkers and targets for therapy. **Methods:** Hybrid-capture based CGP of treatment-naive tissue samples (n = 205) was performed on 3 cohorts of pts with MIBC: i) PURE-01 cohort (n = 144), treated with neoadjuvant pembrolizumab ii) NAC cohort (n = 31) iii) therapy-naïve radical cystectomy (RC) cohort (n = 30). Targetable gene alterations (GAs) were assessed according to the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT). A modified version including tumor mutational burden (TMB) (cut off 10 mut/Mb) was used. Logistic models were used to analyze associations with pathologic complete response (pCR, pT0N0) or downstaging (pT≤1). Kaplan-Meier method was used to estimate event free survival (EFS) and distant relapse free survival (DRFS). Univariable Cox regression analyses were run. **Results:** ESCAT tier ≥3A alterations were found in 164 (80%) pts in total and in 134 (65%) when TMB was excluded. 15% of pts had tier 1B GAs (*FGFR3* mutations [mut] or fusion), 54% tier 1C (TMB≥10 mut/Mb), and 16% had tier 2B GAs. Tier 3A GAs were found in 52% pts. *ERBB2* amplification (8%) and *ERBB3* mut (7%) were the most frequent tier 2B GAs. *PIK3CA* (24%) and *ERBB2* mut (14%), followed by *ATM* (7%), were the most represented tier 3A GAs. In the PURE-01 cohort, TMB≥10 mut/Mb was significantly associated with pCR and downstaging at univariable and multivariable analyses. Univariable Cox regression analyses did not show association between TMB and EFS or DRFS. *ERBB2/ERBB3* GAs were associated with TMB≥10 (p = 0.003 in entire population, p = 0.048 in PURE-01 cohort). However, in the PURE-01 cohort there was no association between *ERBB2/ERBB3* GAs and response. In the NAC cohort, pCR rate was 27% in pts with TMB≥10 while none with TMB < 10 had pCR (p = 0.6). Downstaging was 55% in TMB≥10 vs 40% in TMB < 10 (p = 0.7). DRFS did not show significant difference according to TMB (p = 0.6). In the PURE-01 cohort, pCR rate and downstaging were numerically higher in pts with homologous recombination repair alterations (HRR+), but there was no significant association (p = 0.3). No association was found between HRR status and EFS or DRFS. In the NAC cohort pCR was 33% in HRR+ vs 19% in HRR- (p = 0.6). There was no difference in downstaging. At median follow-up of 19.2 months, mDRFS was longer in HRR+ vs HRR- (mDRFS NE vs 27.9 months p = 0.039). **Conclusions:** CGP identified GAs which potentially predict benefit from approved or investigational treatments or provide rational for clinical trial evaluation in a high proportion of pts. TMB≥10 was associated with response to pembrolizumab, while HRR GAs with DRFS after NAC. Cases with *ERBB2/3* GAs featured higher TMBs but were not associated with response to immunotherapy. Research Sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori; Foundation One Inc.; PURE-01 study funding: Merck & Co., Inc., Kenilworth, NJ, USA; Associazione Italiana per la Ricerca sul Cancro (AIRC).

480 Poster Session, Thu, 8:00 AM-6:30 PM and Poster Highlights Session; Displayed in Poster Session

Characterization of *FOXF1* as a novel regulator of nodal metastasis in bladder cancer.

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Background: Members of the forkhead transcription factor (FOX) family are important mediators of embryonic development and are known to be altered in a variety of cancers. The functional role of *FOXF1* in bladder tumorigenesis and progression has not been clearly characterized thus far. This study investigated the clinical implications of differential *FOXF1* expression in bladder cancer, and potential mechanisms by which its alteration can lead to tumor metastasis. **Methods:** Whole genome expression profiling was performed on paired primary tumors and nodal metastases from a radical cystectomy discovery cohort using Illumina HT12 v3-4 BeadChip arrays to identify *FOXF1* as a top differentially expressed gene. Prognostic role of differential *FOXF1* expression was validated on two independent cystectomy cohorts. Differential *FOXF1* expression was also evaluated in murine orthotopic xenografts. Small interfering RNA was used to knock down *FOXF1* in RT112 and UC6 bladder cancer cell lines to develop an *in vitro* model for assessment of metastatic potential. Next-generation sequencing and hierarchical clustering analysis were used to identify differentially altered genes secondary to *FOXF1* knockdown. 186 biologically curated pathways were interrogated with internal validation to elucidate the downstream biologic mechanisms of metastasis. **Results:** In the discovery cohort, *FOXF1* was a top differentially expressed gene with 3.6-fold lower expression in nodal metastases than paired primary tumors ($n = 33$, $p < 0.001$). Multivariable analyses in two validation cohorts (total $n = 128$) indicated that *FOXF1* underexpression was associated with worse cancer-specific ($p = 0.046$) and overall survival ($p = 0.006$). Murine orthotopic xenografts ($n = 13$) established from human bladder cancer cell lines (UC3, UC6, UC14) showed *FOXF1* underexpression in metastatic deposits compared with primary tumors ($p = 0.004$). Hierarchical clustering identified 40 differentially expressed genes between *FOXF1*-knockdown bladder cancer cell lines and their corresponding controls. Biological pathway interrogation showed differential enrichment for genes associated with mitogen-activated protein kinase signaling, focal adhesion and other carcinogenic pathways in *FOXF1*-knockdown cells compared with controls (normalized enrichment score ≥ 1.3). **Conclusions:** We identify and characterize *FOXF1* as a novel regulatory molecule that potentially drives bladder cancer metastasis. This may be modulated through alterations in intracellular signaling and cellular adhesion. *FOXF1* may serve as a prognostic biomarker that can identify patients at impending risk for metastasis who may benefit from more aggressive management. Research Sponsor: U.S. National Institutes of Health.

HPV-16 positive clinically advanced squamous cell carcinoma of the urinary bladder (mBSCC): A comprehensive genomic profiling (CGP) study.

Joseph M Jacob, Philippe E. Spiess, Gennady Bratslavsky, Andrea Necchi, Petros Grivas, Natalie Danziger, Douglas I. Lin, Richard Huang, Douglas A Mata, Brennan James Decker, Ethan Sokol, Jeffrey S. Ross; SUNY Upstate Medical University, Syracuse, NY; Moffitt Cancer Center, Tampa, FL; SUNY Upstate University Hospital, Bethesda, MD; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; University of Washington, Seattle, WA; Foundation Medicine, Inc., Cambridge, MA; Foundation Medicine, Cambridge, MA; Foundation Medicine, Inc, Morrisville, NC; Foundation Medicine Inc., Cambridge, MA

Background: mBSCC is an uncommon form of urinary bladder malignancy when compared with the much higher urothelial carcinoma incidence. We studied the genomic alteration (GA) landscape in a series of mBSCC based on the association with HPV-16 to determine if differences would be observed between the positive and negative groups. **Methods:** Using a hybrid capture-based FDA-approved CGP assay, a series of 171 mBSCC were sequenced 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. PD-L1 expression was determined by IHC (Dako 22C3) with low tumor cell positive staining set at 1-49% and high staining at ≥50% expression. **Results:** Overall, 11 (6.4%) of the mBSCC were found to harbor HPV-16 sequences (Table). HPV-16+ status was identified slightly more often in women (NS) and in younger patients (P = .04); 2 female patients with mBSCC had prior history of SCC including 1 anal SCC and 1 vaginal SCC. HPV-16+ mBSCC had fewer GA/tumor (P < .0001), and fewer inactivating GA in *CDKN2A* (P < .0001), *CDKN2B* (P = .05), *TERT* promoter (P = .0004) and TP53 (P < .0001). GA in genes associated with urothelial carcinoma including *FGFR2* and *FGFR3* were similar in both HPV-16+ and HPV-16- mBSCC groups. MTOR and PIK3CA pathway GA were not significantly different in the 2 groups. MSI and TMB were also similar in the 2 groups. The 3 HPV-16+ mBSCC cases showed high positive PD-L1 IHC staining. **Conclusions:** HPV-16+ mBSCC tends to occur more often in women and younger patients. As reported in other HPV-associated squamous cell carcinomas, HPV-16+ mBSCC demonstrates significantly reduced frequencies of inactivating mutations in cell cycle regulatory genes with similar GA in MTOR and PIK3CA pathways. The implication of HPV in the pathogenesis of bladder cancer remains unknown but warrants further exploration and clinical validation. Research Sponsor: Foundation Medicine Inc.

mBSCC	HPV-16 +	HPV-16 -	Significance
Number of Cases	11	160	
Gender (%female)	55%	50%	NS
Median age (range) years	56 (35-75)	64 (30-89)	-
Mean age (years)	54.4	63.8	P = .04
GA/tumor	4.8	8.5	P < .0001
BRCA1	9%	1%	NS
BRCA2	0%	2%	NS
***CCND1* amplification**	0%	20%	NS
***CD274* amplification**	0%	2%	NS
***CDKN2A* inactivation**	9%	71%	P < .0001
***CDKN2B* inactivation**	0%	41%	P = .05
***EGFR* amplification**	9%	7%	NS
FBXW7	9%	11%	NS
FGFR2	9%	0%	NS
FGFR3	9%	9%	NS
NOTCH1	0%	9%	NS
PIK3CA	55%	38%	NS
***PTEN* inactivation**	18%	8%	NS
***TERT* promoter mutation**	18%	74%	P = .0004
TP53	9%	78%	P < .0001
MSI High	0%	1%	NS
Median TMB	6.1	6.3	NS
TMB≥10 mut/Mb	27%	26%	NS
TMB≥20 mut/Mb	9%	11%	NS
PD-L1 Low Positive	0% (3 cases)	40% (52 cases)	-
PD-L1 High Positive	67% (3 cases)	19% (52 cases)	-

Multi-omics prognosis predictive model of metastatic urothelial carcinoma (mUCs) with immunotherapy.

Ning He, Yiqun Zhang, Yadong Yang, Jianfei Wang; GloriousMed Clinical Laboratory (Shanghai) Co., Ltd., Shanghai, China

Background: A fraction of mUCs patients can occur robust and durable responses in metastatic urothelial cancer patients treated with anti-PD-L1 agent (atezolizumab), and prognosis of immunotherapy exhibited a lack of attention. We aim to develop an effective prognosis for mUCs patients' immunotherapy management. **Methods:** Public omics and clinical data of patients were collected from R package "IMvigor210CoreBiologies" (348 samples with RNA sequencing data, and 293 samples with DNA sequencing data). Immune cell infiltrations in the tumor microenvironment were quantified by single sample Gene Set Enrichment Analysis (ssGSEA). Prognosis model were trained by elastic net Cox proportional hazards algorithm, 10-fold Cross Validation were used for avoiding over fitting. Statistical analysis, survival analysis and data visualization were all carried out using the R. **Results:**Based on the whole transcriptome, whole exome sequencing, data were processed into five class parameters (including immunohistochemical, gene mutation, gene expression, signature score and molecular subtyping). With regularized Cox regression analysis, 17 genes (CXCL9, GJB2, THBD, SEPT3, PLTP, LDLR, PPM1H, ACVR1C, MT1G, MT1L, ANXA2, LOC102725117, PCDHGB7, MCF2L2, APOL6, ITGAV, PCDH11X) were selected for evaluating mRNA expression level risk score, 11 immune cells (TIS, TGF_{β}, Activated CD8+ T cell, Central memory CD4+ T cell, Central memory CD8+ T cell, Effector memory CD4+ T cell, Gamma delta T cell, Memory B cell, Eosinophil, Immature dendritic cell, Monocyte neutrophil) were selected for evaluating pathway level risk score. Then we combined mRNA risk score, signature risk score, gene mutations, PD-L1 IHC, TMB and other clinical parameters for further dimension reduction. Finally, PD-L1 in tumor-infiltrating immune cells (ICs) (HR = 0.75, 95% CI 0.64-0.89, $p < 1e-03$), mRNA risk score (HR = 3.06, 95% CI 2.42-3.86, $p < 1e-06$) and TMB (HR = 0.75, 95% CI 0.64-0.89, $p < 1e-03$) were selected for Cox-model. Samples were divided into groups were by median of risk score, and there were significant difference of overall survival between high-risk and low-risk group, in training dataset ($p < 1e-04$, $AUC_{(t = 6m/12m/18m)}$ = 0.69/0.79/0.80) and validation dataset ($p < 1e-04$, $AUC_{(t = 6m/12m/18m)}$ = 0.77/0.82/0.85). In addition, high risk group was less response to PD-L1 immunotherapy than low risk group in our research (χ^2 test, $p < 2.23e-06$). **Conclusions:** Wefirstlyconstructed a multi-omics prognosis prediction model for mUCs with immunotherapy, which may be related to different prognosis and immunotherapy response. This result may help further understanding the anti-immunotherapy of mUCs patient's management. Research Sponsor: None.

Transcriptome analysis of low-risk and high-risk non-muscular invasive bladder cancer patients to reveal disease progression related genes.

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Background: According to the EAU prognostic risk classes, non-muscle invasive bladder cancer (NMIBC) is divided into low, medium, and high risk. Patients with high-risk NMIBC (T1/Tis, with high grade/G3, or CIS) represent a challenging group as they are at greater risk of recurrence and progression.Our specific aim was to investigate the biomarkers associated with progression and recurrence in NMIBC. **Methods:** Tumor tissue were collected from 70 patients with bladder cancer, including high-risk NMIBC (n = 44),low-risk NMIBC (n = 10) and (n = 16) MIBC. mRNA sequenced using the ABclonal Whole RNA-seq Lib Prep kit.The differentially expressed genes were identified using DESeq2 and the analysis of the association between genes expression and patient survival with NMIBC cohorts data(Jakob et al., 2016). RNAseq data of human bladder cancer cell lines were achieved from the Cell Model Passports website (https://cellmodelpassports.sanger.ac.uk/). **Results:**A total of 456 genes are significantly high expressed in high-risk NMIBC group compared with the low-risk NMIBC group. Combined with MIBC expression data,we found 16 genes with consistently increasing expression from the low-risk NMIBC group to high-risk NMIBC group and MIBC group using a fold change of at least 2, and a false discovery rate (FDR) of 0.05.Among these genes,14 genes were also highly expressed in human bladder cancer cell lines. Survival analysis by Kaplan-Meier,we finally identified 13 high-expressed genes, including KRT6A、SPHK1、S100A9、SLC16A1、CDC25B、NELL2、PREX1、C15orf48、AKR1B10、CERCAM、PKMYT1、UCHL1、SLC16A1, were significantly associated with poor progression-free survival($p<0.05$). **Conclusions:** We identified a set of 13 genes that may predict the progression of NMIBC and may serve as molecular targets for NMIBC therapy. these study results need to be confirmed in larger research studies. Research Sponsor: None.

Single cell RNA sequencing of upper tract urothelial carcinoma to reveal significant heterogeneity of the tumor and immune microenvironment.

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Background: Upper tract urothelial carcinoma (UTUC) comprises 5-10% of urothelial malignancies but demonstrates unique clinical and molecular characteristics compared to urothelial carcinoma of the bladder. Prior investigations have used bulk profiling of tumor tissue to identify molecular subtypes, classifying the majority of UTUC as luminal and T-cell depleted. However, bulk sequencing does not allow for analysis of the significant heterogeneity known to be present in urothelial tumors. Single-cell RNA sequencing (scRNA-seq) allows examination of intra-tumoral heterogeneity, clonality, and the complex interactions of the immune tumor microenvironment (TME). We sought to apply this technology to better characterize UTUC and the TME. **Methods:** Single cell RNA sequencing (scRNA-seq) was performed on nine UTUC tissue specimens from six different patients collected fresh via ureteroscopic biopsy using an established institutional process and the 10X Genomics platform. Sequencing reads were normalized and analyzed using R/Seurat package. We assessed the composition of each tumor specimen with known marker genes for molecular subtypes (luminal, basal, squamous, EMT, and claudin-low). We then assessed the composition of immune cells in each specimen using known marker genes. We compared high- and low-grade specimens by subtype composition and immune cell infiltrates. **Results:** Lineage density analyses demonstrate the intra- and inter-tumoral heterogeneity of the nine endoscopic samples analyzed by molecular subtype composition. There is higher expression of luminal and claudin-low subtypes across all samples. The high-grade samples have higher expression of squamous markers. There is significant heterogeneity of immune cell infiltrates in seven specimens (two specimens were excluded due to low CD45+ cell counts). There is higher macrophage infiltration in high-grade samples, which was the only significant difference (Wilcoxon two-sided p-value = 0.05). **Conclusions:** This is the first known study using scRNA-seq expression analysis to characterize the notable heterogeneity of high and low-grade UTUC and the associated TME. Lineage density analysis demonstrates high luminal gene expression across samples, which has been demonstrated on prior bulk sequencing studies. The immune TME is also heterogeneous, with notable increased infiltration of macrophages in high-grade disease. There are unique limitations to performing and analyzing scRNA-seq of fresh UTUC tissue specimens, thus data should be interpreted cautiously. However, this study demonstrates the marked heterogeneity of UTUC tumors and frames our current approaches to bulk molecular subtyping of urothelial cancers and immune deconvolution. Further high-resolution studies are needed to characterize UTUC and inform bulk-sequencing efforts. Research Sponsor: Thompson Family Foundation, Other Foundation.

Novel synthetic lethality (SL) anti-cancer drug target in urothelial bladder cancer (UCB) based on *MTAP* genomic loss: Incidence and correlations in standard of care (SOC).

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Background: When UCB presents or progresses to chemorefractory metastatic disease, the search for new therapy targets is paramount. Targeting PRMT5 arginine methyltransferase accumulation in tumors with *MTAP* (methylthioadenosine Phosphorylase) genomic loss has been proposed as a new SL based anti-tumor strategy and under consideration for development for UCB. We sought to evaluate the incidence of patients with candidate SL and correlate to treatment-guiding biomarkers currently evaluated in SOC. **Methods:** 2,683 cases of clinically advanced UCB underwent hybrid-capture based comprehensive genomic profiling in a standard of care setting using the F1CDx FDA-approved assay to evaluate all classes of genomic alterations (GA) among 324 genes. Tumor mutational burden (TMB) was determined on 0.8 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 95 loci. PD-L1 expression was determined by IHC (Dako 22C3). **Results:** 650 (24%) of UCB feature *MTAP* loss (MTAP-) (Table). The gene and age distributions were similar *MTAP* intact (MTAP+) and MTAP- UCB. The GA/tumor was higher in MTAP- UCB likely reflecting the significant GA co-deletions of *CDKN2A/B* at the 9p21 locus. Of potential therapeutic targets, *FGFR3* and *PTEN* GA were more frequent in the MTAP- UCB. In contrast, biomarkers of immunotherapy (IO) response included higher frequencies of high TMB and high PD-L1 IHC staining in the MTAP+ UCB. **Conclusions:** When compared with MATP+ UCB, MTAP- UCB differs in genomic signatures including an increase in potential for targeted therapies but a lower potential for IO drug benefit. Thus, the genomic landscape in MTAP- UCB may play a significant role in the design of clinical trials incorporating SL strategies when targeting PRMT5 in MTAP deficient tumors. Research Sponsor: Foundation Medicine Inc.

	UCB MTAP Intact	UCB MTAP Loss	Significance
Number of Cases	2,033	650	
Males/Females	77%/23%	72%/28%	NS
Median age (range) years	70 (16-95)	71 (31-98)	NS
GA/tumor	7.4	9.9	
CDKN2A	18%	99.8%	P<.0001
CDKN2B	8%	96%	P<.0001
TP53	66%	42%	P<.0001
TERT	75%	79%	NS
FGFR3	13%	33%	P<.0001
PIK3CA	21%	26%	NS
ERBB2	18%	14%	NS
EGFR	4%	4%	NS
PTEN	4%	6%	P=.04
TSC1	7%	2%	P<.0001
BRCA1/2	2%/0%	1%/2%	NS
MSI High	1%	1%	NS
Median TMB	7.5	6.3	
Mean TMB	11.2	8.5	P<.0001
TMB>10 mut/Mb	41%	30%	P<.0001
TMB>20 mut/Mb	15%	7%	P<.0001
PD-L1 Low Positive	20%	24%	NS
PD-L1 High Positive	22%	3%	P<.0001

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Circulating tumor DNA analysis of genomic alterations in metastatic urothelial carcinoma from NCT03113266 study.

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Background: Recent studies have suggested the predictive value of liquid biopsies for immune checkpoint inhibitors. NCT03113266 is a multicenter phase II trial to evaluate the safety and efficacy of toripalimab (anti-PD-1) in metastatic urothelial carcinoma (mUC). Here we report the initial circulating tumor DNA (ctDNA) analysis of genomic alterations from a single-institution biomarker cohort. **Methods:** Twenty-seven mUC patients receiving toripalimab (3 mg/kg Q2W) at Ren Ji Hospital were enrolled and consented to Institutional Review Board-approved protocols permitting biomaterial collection and genetic sequencing. Serial plasma specimens were obtained at baseline and every two cycles. The 600-gene panel (PredicineATLAS) liquid biopsy assay was applied to assess somatic variants and blood tumor mutational burden (bTMB). **Results:** The ctDNA assays were performed successfully for 100% of baseline samples (n = 27) with average read depth of 24,389 (range 14,000-31,700). A total of 571 non-synonymous mutations were identified, demonstrating prevalent aberrations in *TP53* (63%), *TERT* promoter (30%), *KDM2D* (26%), *PPM1D* (26%), and *KDM6A* (26%). In 5 patients, *FGFR3* variants were detected, including 6 missense sites and 4 *FGFR3-TACC3* fusion events. Copy number gain (*FGFR1*, *ERBB2*) and loss (*PTEN*, *BRCA2*, *CDKN2A*) were pinpointed. TMB estimation revealed one case with an exceptionally high bTMB (62.6 mutations/Mb) and genomic features of microsatellite instability (MSI). Concordance with tumor-based genotyping and ctDNA kinetics during toripalimab treatment are being determined. **Conclusions:** Prospective ctDNA analysis using the PredicineATLAS liquid biopsy assay is feasible and represents a minimally invasive approach to detecting cancer-specific genetic landscape and potentially guiding personalized therapeutic decisions in mUC patients. Clinical trial information: NCT03113266. Research Sponsor: Shanghai Junshi BioSciences; Huidu Shanghai Medical Sciences Ltd.

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Efficacy of immune checkpoint blockade in patients with advanced upper tract urothelial cancer and mismatch repair deficiency or microsatellite instability (MSI).

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Background: Tumors deficient in DNA mismatch repair (dMMR) exhibit a microsatellite unstable phenotype characterized by high tumor mutational burden and an immunogenic tumor microenvironment. Despite the histology-agnostic approval of pembrolizumab for advanced dMMR/MSI cancers, responsiveness of dMMR/MSI upper tract urothelial cancers (UTUC) to immune checkpoint (IC) blockade remains largely unknown. **Methods:** Consecutive records of patients (pts) from a single institution with locally advanced unresectable or metastatic dMMR/MSI UTUC who received IC therapy were analyzed. The primary endpoint was assessment of objective response rate (ORR) using RECIST v1.1. Secondary endpoints were progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier technique. dMMR/MSI status was evaluated by immunohistochemistry (IHC) and/or polymerase chain reaction (PCR). **Results:** Ten pts were identified with locally advanced unresectable (N = 3) or metastatic (N = 7) dMMR/MSI UTUC who received therapy with IC blockade (pembrolizumab = 7, nivolumab = 2, atezolizumab = 1). Median age was 65.5 (range = 46 – 90). Six pts were male. Seven pts had germline dMMR. MSI was detected by PCR in three pts and dMMR by IHC in seven pts (PMS2/MLH1 loss = 4, MSH2 loss = 1, MLH1 loss = 1, MSH6 loss = 1). Five pts received systemic chemotherapy (2 cisplatin based, 1 carboplatin based, 2 other) prior to IC therapy with two pts (40%) achieving partial response (PR). At a median follow-up of 15.5 months (range: 2 – 43 months), all pts were alive, and none experienced disease progression. PFS and OS at 15.5 months were 100%. The observed ORR was 90% (CI, 55.5%, 99.8%), including 8 pts who achieved complete remission (CR). The median time to best response was 4 months (range: 2 – 8 months). Toxicity leading to treatment discontinuation: 1 (grade 3) pancytopenia, 1 (grade 2) pneumonitis, 1 (grade 2) SICCA-like symptoms. **Conclusions:** Immunotherapy with IC inhibitors demonstrates excellent clinical activity in advanced dMMR/MSI UTUC. Further studies integrating these agents earlier in the disease course are warranted in this rare but important subgroup. Given the extremely high complete response rate in this population consideration of preference to IC therapy as initial therapy should be entertained if these findings are validated. Research Sponsor: None.

Combinatorial biomarkers to predict responses to immune checkpoint therapy in metastatic urothelial cancer.

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Background: Immune checkpoint therapy can produce durable anti-tumor responses in metastatic urothelial carcinoma (mUCC); however, the responses are not universal. Despite multiple approvals of immune checkpoint therapy in mUCC, we lack predictive biomarkers to guide patient selection. Therefore, there is a critical need to develop clinically useful biomarkers to refine patient selection. The single biomarker studies either focused on tumor mutations or immune response biomarkers, which may limit predictive power due to lack of integration between cancer cell biology and immune cell responses. The identification of biomarkers may require interrogation of both the tumor mutational status and the immune microenvironment. **Methods:** We performed retrospective multi-platform immuno-genomic analyses of pre-treatment tumor tissues in a discovery cohort (n = 31). Next, we tested the clinical relevance of *ARID1A* mutation and pre-treatment CXCL13 expression in two independent confirmatory cohorts (CheckMate275 and IMvigor210). Additionally, we performed reverse translational studies using murine model of bladder cancer to demonstrate direct association of the biomarkers in anti-PD-(L)-1 mediated anti-tumor immunity. **Results:** We identified genomic mutation of AT-rich interactive domain-containing protein 1A (*ARID1A*) in tumor cells and expression of immune cytokine CXCL13 in the pre-treatment tumor tissues as two predictors of clinical responses. We found that *ARID1A* mutation and expression of CXCL13 in the baseline tumor tissues correlated with improved overall survival (OS) in both confirmatory cohorts (CheckMate275, CXCL13 data, n = 217; ARID1A data, n = 139, and IMvigor210, CXCL13 data, n = 348; ARID1A data, n = 275). Further, reverse translational studies revealed that $CXCL13^{-/-}$ tumor-bearing mice were resistant to immune checkpoint therapy whereas *ARID1A* knockdown enhanced sensitivity to immune checkpoint therapy in a murine model of bladder cancer. We then interrogated CXCL13 expression plus *ARID1A* mutation as a combination biomarker in predicting response to immune checkpoint therapy in CheckMate275 and IMvigor210. Combination of the 2 biomarkers in baseline tumor tissues showed improved OS compared to either single biomarker. **Conclusions:** Cumulatively, this study revealed that the combination of CXCL13 plus *ARID1A* mutation may improve patient selection in mUCC for immune checkpoint therapy. Research Sponsor: Parker Institute of Cancer Immunotherapy.

Association between tumor mutational burden (TMB) and immune-related adverse events (irAEs) in patients (pts) with metastatic urothelial carcinoma (mUC) during checkpoint immunotherapy.

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Background: Immune checkpoint inhibition (ICI) has greatly improved clinical outcomes for pts with mUC and other cancers. ICI is associated with a class of AEs, deemed irAEs due to immune activation. Nonetheless, biomarkers associated with irAE are still lacking. We hypothesized that the immune response against neoantigens is partly responsible for irAEs and investigated the association between irAEs, TMB and response to ICI. **Methods:** We identified patients with mUC at Dana Farber Cancer Institute who were treated with ICI (monotherapy or combination) and had available tumor sequencing data through Oncopanel. TMB was calculated using the number of non-synonymous exonic mutations per megabase. The severity of irAEs was graded using CTCAE v.5.0. Mann-Whitney U test was performed to identify association between TMB, incidence and grade of irAEs. A cut-off of 10/mb was assigned for TMB. Fisher's exact test was used to evaluate the radiologic response between pts with and without irAEs and low vs. high TMB. Multivariable linear regression was used to assess the relationship between TMB, irAEs and response. p-values were adjusted using Benjamini-Hochberg method. **Results:** Of 101 pts with mUC who met the inclusion criteria, 32 (32%) reported irAEs. 6 (6%) were grade (G)1, 20 (20%) were G2, and 6 (6%) were G3. Median(m) time on therapy was 84 days for pts without irAEs and 88 days for pts with irAEs. Pts with irAEs had higher mTMB (15.4/mb) compared to pts with no irAEs (9.8) ($p = 0.01$). In pts on monotherapy (93), those with irAEs (n=27) had a higher mTMB (15.13/mb) compared to pts with no irAEs (n=66) (mTMB = 10.20/mb) ($p = 0.01$). Out of 94 pts with radiological data, response was achieved in 16 (50%) pts with irAE vs 10 (16%) pts with no irAE ($p < 0.001$). When both irAE and response were included in a multivariable regression, the association between irAE and TMB was not significant ($p = 0.4$). Pts with both irAE and high TMB had a response rate of 56% which was significantly higher than those with either irAE but low TMB (28.6%) or high TMB but no irAE (21.2 %) or low TMB and no irAE (10.3%) (Chi-square test $p = 0.002$; FDR corrected p-values for individual comparisons in Table). There was no association between TMB and irAE grade. **Conclusions:** Higher TMB was associated with higher incidence of irAEs in pts with mUC on ICIs. Moreover, pts with both high TMB and irAEs exhibited better response rates than those with only high TMB or irAEs, suggesting that they may provide complementary tumor and host characteristics. Further evaluation in mUC is needed to confirm this relationship between TMB, irAEs and response in a larger cohort and explore specific mutational signatures that may be associated with irAEs. Research Sponsor: None.

	Low TMB/No irAE	Low TMB/irAE	High TMB/No irAE	High TMB/irAE
Low TMB/No irAE	-	0.5	0.5	0.02
Low TMB/irAE	-	-	0.6	0.5
High TMB/No irAE	-	-	-	0.04
High TMB/irAE	-	-	-	-

Integrated clinicopathologic and molecular risk stratification for disease recurrence in muscle-invasive bladder cancer.

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Background: Integrating molecular subtypes, gene transcripts associated with disease recurrence (DR), and clinicopathologic features may help risk stratify muscle-invasive bladder cancer (MIBC) patients & guide therapy selection. We hypothesized that combined transcriptomic & clinical data would improve risk stratification for DR (local or distant) after cystectomy +/- adjuvant chemotherapy. **Methods:** We identified 401 MIBC patients (pT2-4 N0-N3 M0) in The Cancer Genome Atlas with detailed demographic, clinical, pathologic, and treatment-related data. We split the data into training (60%) & testing (40%) sets. We produced RNA gene expression scores for molecular subtype using 48 established, relevant genes (PMID 28988769). In the training set, we performed feature selection by conducting random forest modeling of an additional 108 genes associated with DR. We kept genes of highest importance based on the evaluation of increasing mean-squared error & node purity. We excluded highly correlated genes & used the false discovery rate method for multiple hypotheses testing. We performed univariable analyses on genes of highest importance, molecular subtype, & clinicopathologic variables. Using adjusted multivariable analyses (MVA), we built two models: with & without transcriptomic data. Using the testing set, we compared the final models' performance to predict DR, using receiver operating characteristics & area under the curve (AUC). **Results:** Median follow-up was 18 months (range 1-168). 104 patients recurred with a 5-yr cumulative incidence of 34.6%[28.6-40.5%]. Using the training set, we identified 6 genes significantly associated with DR (VEGFA, TRMT1, FGFR2B, ERBB2, MMP14, PDGFC). The final MVA showed that the new 6-gene signature (HR 1.61, 95% CI 1.27-2.05, $p < 0.001$); immune molecular subtype [increased expression of PD-L1, PD-1, IDO1, CXCL11, L1CAM, SAA1] (HR 0.52, 95% CI 0.29-0.94, p = 0.03); smoking status (HR 1.17 per 10 pack-years, 95% CI 1.05-1.29, p = 0.005); and local failure risk factors [$\geq$pT3 with negative margins & $\geq$10 nodes removed (HR 1.63, 95% CI 1.15-2.32, p = 0.006); $\geq$pT3 and positive margins OR $<$ 10 nodes removed (HR 3.26, 95%CI 2.43 to 4.09, p = 0.007)], were all significantly associated with DR. This combined model outperformed a standalone clinicopathologic model (AUC 0.75 vs. 0.66) in the testing set. The combined model stratified patients based on DR risk into 3 groups with 5-yr cumulative incidences of 19.8%[7.7-31.9%] (low-risk); 34.5%[26.1-42.8%] (intermediate); and 49.8%[37.7-61.9%] (high), Gray's Test $p < 0.0001$. **Conclusions:** To our knowledge, this study is the first to integrate clinicopathologic & transcriptomic information (including molecular subtype) to better stratify MIBC patients by risk of recurrence. This stratification may help guide decision-making for adjuvant treatment. Further validation is warranted. Research Sponsor: None.

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Superior molecular pathology of urothelial bladder cancer using urinary cell-free DNA.

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Background: Both urinary and blood cell-free DNA (cfDNA) have been implicated in noninvasive detection and surveillance of urothelial bladder cancer (UBC). However, a direct comparison of their diagnostic performance in the real-world setting is lacking. **Methods:** 59 eligible cases with pathologically confirmed disease and accompanying tissue/urine pairs were prospectively enrolled and consented to Institutional Review Board-approved protocols. Baseline peripheral blood mononuclear cell (PBMC) and plasma specimens were collected during clinic visit. The 180-gene Predicine liquid biopsy assay was applied for ultra-deep targeted sequencing and somatic alteration identification in tumor tissue-based DNA (tDNA), urinary cfDNA (ucfDNA) and blood cfDNA (bcfDNA). **Results:** The 59 studied subjects constituted a natural UBC cohort of non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC), including 48 (81.4%) NMIBC and 42 (71.2%) male patients. Diverse quantitative metrics such as VAF (variant allele frequency) and TMB (tumor mutational burden) were invariably concordant between tDNA and ucfDNA, but not bcfDNA. The mutational landscape captured by tDNA or ucfDNA highly resembled each other and mirrored previously described genomic panorama of UBC, whereas a significant proportion of bcfDNA aberrations stemmed from clonal hematopoiesis. Using tDNA-informed variants as the ground truth, ucfDNA assays achieved a specificity of 99.3%, a sensitivity of 86.7%, a positive predictive value (PPV) of 67.2%, a negative predictive value (NPV) of 99.8%, and a diagnostic accuracy of 99.1%, which were generally lower in the case of bcfDNA analysis. **Conclusions:** Urine-based molecular pathology provides valid and complete genetic information about neoplastic lesions, and represents a faithful surrogate for genotyping and monitoring UBC. Research Sponsor: Huidu Shanghai Medical Sciences Ltd.

Patient-centric care in bladder cancer: Virtual simulation to benefit clinical decision-making of oncologists.

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Background: Immunotherapy (IO) utility in bladder cancer (UC) has expanded into multiple stages of disease. Employing IO optimally requires mastery of clinical trial data, patient eligibility criteria, and interpretation of biomarkers and determination of treatment sequencing. Given the nuanced therapeutic decision-making, education was developed in partnership between Medscape Oncology and Society for Immunotherapy of Cancer (SITC) to assist oncologists in improving their performance surrounding the management of patients with advanced UC. **Methods:** A virtual patient simulation (VPS) continuing medical education (CME)-certified activity depicting 2 advanced UC cases was made available to oncologist members of Medscape. The cases depicted 1) a patient with newly diagnosed metastatic UC with comorbidities and PDL1+ disease and 2) a patient with advanced UC progressing on platinum therapy with no actionable mutations. The VPS platform captures real-life decision making process of oncologists in an EHR-like format supported by an extensive database of diagnostic and treatment possibilities. Learners were able to interact with patients via video, order lab tests, assess patients, make diagnoses, and order treatments matching the scope and depth of actual practice. Tailored clinical guidance (CG) employing up-to-date evidence-based and faculty recommendations was provided after each decision point. Decisions were collected pre- and post-CG and analyzed using McNemar's test to determine p-values. Data were collected from 4/28/20 to 7/13/20. **Results:** Analyses from oncologists (n = 51-66) found significant improvement in performance measured pre- to-post CG: Case 1: Ordering appropriate testing to determine patient eligibility for therapy (39% pre; 65% post; $p < .001$) Prescribing appropriate therapy based on patient- and disease-specific factors (38% pre; 77% post; $p < .001$) Providing appropriate counseling and follow-up for a patient receiving treatment (65% pre; 80% post; $p < .01$) Case 2: Ordering appropriate testing to determine patient eligibility for therapy (39% pre; 57% post; $p < .01$) Prescribing appropriate therapy based on patient- and disease-specific factors (25% pre; 41% post; $p < .01$) Providing appropriate counseling and follow-up for a patient receiving treatment (71% pre; 82% post; $p < .05$). **Conclusions:** This activity demonstrates the value of providing oncologists a simulation platform to practice and master clinical decision-making of the limitless possible diagnostic and therapeutic options in the management of advanced UC. Insights from rationales for each clinical decision point uncover continued gaps for oncologists on guideline recommendations, efficacy outcomes, or molecular implications. They also highlight barriers including limited experience or confidence with IO. Research Sponsor: Bristol Myers Squibb and Merck & Co., Inc. and partnership with Medscape Oncology and Society for Immunotherapy of Cancer.

Impact of primary tumor location, histology, and host factors on objective response to immune checkpoint inhibitors in metastatic urothelial carcinoma.

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Background: Factors affecting response to immune checkpoint inhibitor (ICI) are poorly understood in metastatic urothelial carcinoma (mUC). While tumor PD-L1 status is often used as a biomarker, it is not always predictive and ICI also benefits patients (pts) with PD-L1 negative tumors. Therefore, we sought to study the effect of some host and disease-related variables like gender, ethnicity, body mass index (BMI), platelet to lymphocyte ratio (PLR), and neutrophil to lymphocyte ration (NLR) on objective responses in pts with mUC treated with ICI. **Methods:** We performed a retrospective analysis of adult pts with mUC who received ≥2 cycles of ICI (pembrolizumab or atezolizumab) at the Cleveland Clinic from 2015 to 2020. Tumor and host-related factors evaluated are listed in the table below. We focused on meaningful treatment response, so only partial response (PR) and complete response (CR) were included as responders, while stable disease (SD) and progressive disease (PD) were counted as non-responders. Analysis was carried out with Fisher's exact test and Wilcoxon rank sum test as applicable. **Results:** A total of 124 pts with mUC that received ICI were included. Gender did not correlate with response ($p>0.99$) or duration of response ($p=0.37$). Ethnicity did not correlation with response ($p=0.78$) or duration of response ($p=0.24$). Histology (UC, mixed variant histology or non UC) did not correlate with response ($p=0.13$) or duration of response ($p=0.87$). Location of primary malignancy (upper tract versus lower tract) did not correlate with response ($p>0.99$) or duration of response ($p=0.36$). BMI ($p=0.23$), PLR ($p=0.9$), and NLR ($p=0.9$) did not correlate with objective response. **Conclusions:** In our single center experience of pts with mUC treated with ICI, host factors (gender, ethnicity, histology, BMI, NLR, PLR) and location of primary tumor did not correlate with treatment response or duration of response. Although there were few African Americans represented in this study as commonly seen for minority representation, it is encouraging that no significant differences in responses were observed. The role of BMI and gender in response to ICI treatment in mUC was not observed. While there are limitations of a retrospective analysis, our study warrants investigation into predictive factors of response to ICI in mUC. Ongoing work integrating radiomics and pathomics will further our understanding and develop potential predictive biomarkers of response to ICI in mUC. Research Sponsor: None.

Patient and Tumor Characteristics		Total Patients	Responders (CR or PR)	Non-Responders (SD or PD)	p-value
Gender	Female	30	7	23	>0.99
	Male	94	22	72	
Ethnicity	African American/ Black	4	0	4	0.78
	Asian	3	1	2	
	Caucasian/White	106	25	81	
	Hispanic/Latino	5	1	5	
	Unknown	6	2	4	
Histology	Pure Urothelial	69	20	49	0.13
	MIxed	46	7	39	
	Non-Urothelial	5	1	4	
	Unknown	4	1	3	
Tumor Location	Lower Tract	97	23	74	>0.99
	Upper Tract	24	5	19	
	Unknown	3	1	2	

Tumor mutation burden and immune microenvironment analysis of urothelial carcinoma.

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Background: Tumor mutation burden (TMB) has been established as a biomarker for response to immune therapy and prognosis in various cancers. However, the correlation between TMB and immune microenvironment remains unwell studied, especially in urothelial carcinoma. This study was aimed to investigate the relationship between TMB and other immunotherapy related biomarkers, including genetic alterations, APOBEC signature, microsatellite instability (MSI), PD-L1 expression and immune cell infiltration in urothelial carcinoma. **Methods:** 131 patients with urothelial carcinoma admitted from October 2018 to May 2020 were included. Total DNA was isolated from FFPE or fresh tissues. Mutation profiles, APOBEC signature and MSI scores were obtained by next-generation sequencing based a 642 cancer genes panel assay. PD-L1 expression, CD8+ T-cells and tumor-infiltrating lymphocytes density were evaluated by immunohistochemistry. The correlation was analyzed by Wilcoxon signed-rank test. **Results:** The mutation landscape showed that TP53 mutation is the most common alterations (n = 64/131, 48.9%), followed by KMT2D alterations (n = 49/131, 37.4%), KDM6A mutations (n = 42/131, 32.1%), MUC17 mutations (n = 42/131, 32.1%). The median TMB was 5.06 Muts/Mb (0-118 Muts/Mb). 2 of 131 patients showed MSI-H, who exhibited a much higher TMB (41, 118 Muts/Mb). Further analysis showed that TMB in the patients with certain gene mutations (such as TP53, KMT2D, KDM6A and MUC17) was significantly higher than those wild type ones ($p < 0.05$). Meanwhile, the high APOBEC-enrichment group has a higher TMB than the low APOBEC-enrichment group (p = 0.045). Furthermore,we observed that the patients with a higher PD-L1 expression (n = 28/131, 21.4%, at a combined positive score cut-off value of 10) also showed a significantly higher TMB (p = 0.016), and TMB in the patients with higher density of CD8+ T-cells (n = 42/131, 32.1%, at a cut-off value of 5%) was also significantly higher than that of the group with lower density of CD8+ T-cells (p = 0.039). **Conclusions:** This study provides new insights into the correlation between the TMB and the immune microenvironment in urothelial carcinoma. The result may be a reference to immunotherapy. Research Sponsor: None.

495 **Poster Session**

The impact of adjuvant chemotherapy on oncologic outcomes of patients with locally advanced bladder adenocarcinoma: An analysis of the National Cancer Database.

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Background: The relatively poor prognosis associated with locally advanced bladder adenocarcinoma necessitates investigation of the utility of adjuvant chemotherapy (AC) and risk stratification of those who would benefit from such systemic therapy. This study seeks to evaluate the oncologic and surgical outcomes of those with locally advanced disease treated with and without AC. **Methods:** A retrospective cohort analysis was performed using the National Cancer Database from 2006 to 2016. Patients with non-metastatic locally advanced pT3-4 or pT(any)N1-3 primary bladder adenocarcinoma who received AC only or did not receive AC after radical (RC) or partial cystectomy (PC) were included. The AC cohort was further sub-stratified by surgery type (PC versus RC) and disease origin (urachal versus non-urachal subtypes). Survival, oncologic, and surgical outcomes were compared between cohorts. **Results:** Inclusion criteria identified 79 AC patients and 251 no AC patients. Of the 79 patients who received AC, 23 had PC procedure, 56 had RC procedure, 10 had urachal origin and 69 had non-urachal origin. Receipt of AC was significantly higher in RC relative to PC (27.6% vs 18.1%; p = 0.049). Urachal vs. non-urachal subtype did not impact receipt of AC (25.3% vs 17.5%; p = 0.214), but urachal subtype was associated with improved overall survival compared to non-urachal (47% vs 18%; HR = 0.37; p = 0.04). Although receipt of AC was significantly associated with higher odds of positive margins (46% vs 23%; odds ratio = 2.85; $p < 0.01$), no difference in overall survival was detected between the AC and no AC cohorts (23% vs 19%; hazards ratio [HR] = 0.98; p = 0.91). Of note, independent of AC, PC was associated with improved survival compared to RC (51% vs 12%; HR = 0.25; $p < 0.01$). **Conclusions:** There is no detected survival benefit to the use of a non-standardized AC regimen in locally advanced bladder adenocarcinoma. Within the AC treated population, survival outcomes suggest that urachal subtype may confer survival advantage and that those patients selected for PC tend to have improved survival. Although employing a national dataset, statistical power was limited given the rarity of this disease. Further investigation is warranted on a larger scale in order to assess the impact of AC regimen, afford proper patient selection, and enhance risk stratification for oncologic outcomes. Research Sponsor: None.

Role of CA 125, CA19-9 and CEA in predicting outcome following neoadjuvant chemotherapy in muscle invasive bladder cancer.

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Background: We have previously shown the prognostic value of three tumor markers (TMs) including Carbohydrate Antigen 125 (CA-125), Carbohydrate Antigen 19-9 (CA 19-9) and Carcinoembryonic Antigen (CEA) in muscle invasive bladder cancer (MIBC). Current report presents an update on TM levels before and after neoadjuvant chemotherapy (NAC) and their association with oncological outcomes. **Methods:** Serum levels of three TMs were prospectively measured in patients with MIBC who underwent NAC between 2011 and 2019. Rate of pathological upstaging (Path-U) and recurrence-free (RFS) was compared between patients with: (1) Elevated versus normal pre-NAC TM (2) Elevated versus normal post-NAC TM, and (3) Elevated pre-NAC TMs with normalized post-NAC TMs (TM responders) versus persistently elevated post-NAC TMs (TM non responders). **Results:** Of a total of 199 patients, 63 patients had both pre- and post-NAC TMs. 33/63 (52%) patients had elevated pre-NAC TM of whom, 15/33 (45%) were TM responders. Patients with elevated pre-NAC TM had significantly higher rate of Path-U compared to those with normal pre-NAC TM (62% vs. 22.5%, respectively; $P < 0.001$). There was no significant difference in Path-U in the other two comparison groups. Patients with elevated pre- and post-NAC TM had significantly lower RFS. Compared to TM responders, TM non responders had significantly higher rate of recurrence (70% vs 34%) and shorter median time to recurrence (4.2 months vs 13.5 months) ($P = 0.03$). In six patients with recurrence who had complete post cystectomy TM, TM recurrence preceded clinical recurrence by median of 1.2 months (IQR 0.8 – 2.4 months). **Conclusions:** Elevated TM prior to NAC is associated with pathologic upstaging. TM elevation pre- or post-NAC predicts a worse outcome. Post-cystectomy TM might play a role in earlier detection of recurrence. Research Sponsor: None.

TPS497 **Trials in Progress Poster Session**

Clinical-pathological characterization and outcomes of metastatic urothelial cancer in Latin America: Retrospective and translational multicenter database (LACOG 1518).

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Background: There is lack of high-quality and comprehensive data on advanced urothelial cancer in Latin America. Pathological and clinical outcomes information of this cancer can help the scientific community to understand the current standard of treatment and identify possible gaps for optimal care. Very few translational studies were performed in advanced urothelial cancer in developing countries describing the prevalence of key biomarkers for targeted agents and immunotherapy. **Methods:** LACOG 1518 is a large multi-institutional retrospective study that will collect information about sociodemographic data, treatment and outcome of patients diagnosed with recurrent/ metastatic urothelial cancer in Latin America between January 2016 and December 2019. Socio-demographic characteristics, clinical-pathological features, treatment patterns and outcomes will be extracted from medical charts. Tumor tissue will be collected for fibroblast growth factor receptor (FGFR) gene mutation or fusion test in a central laboratory. A biorepository will be built for future translational research including PD-L1 test and next generation sequencing. Primary endpoint consists on characterize demographic, socioeconomic factors, medical and oncological history of patients diagnosed with recurrent/metastatic urothelial cancer. This study aim to describe treatment sequence, duration, best response and progression time in each line of therapy as well as survival at 1 and 2 years. Translational research endpoints are biomarkers prevalence and association with treatment responses and outcomes. Research Sponsor: Janssen-Cilag PharmaceuticalLatin American Cooperative Oncology Group.

TPS498 **Trials in Progress Poster Session**

TROPiCS-04: Study of sacituzumab govitecan in metastatic or locally advanced unresectable urothelial cancer that has progressed after platinum and checkpoint inhibitor therapy.

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Background: Treatment options are limited for patients with locally advanced unresectable or metastatic urothelial carcinoma (mUC) who progress following prior platinum-based and checkpoint inhibitor (CPI) therapy. Sacituzumab govitecan (SG) is an antibody-drug conjugate consisting of an anti–Trop-2 monoclonal antibody coupled to SN-38 (an active metabolite of irinotecan, a topoisomerase-I inhibitor) via a unique hydrolyzable linker. A phase II registrational study, TROPHY-U-01 study, confirmed the initial positive efficacy signal in mUC. SG demonstrated an objective response rate (ORR) of 27% and median overall survival (OS) of 10.5 months in patients with mUC (median 3 prior lines of therapy and 87% with ≥1 Bellmunt risk factors) who progressed after prior platinum-based and CPI therapies (n=113; Loriot ESMO 2020). The results compared favorably with historic single-agent chemotherapy (ORR ~10%; OS ≤7 months). A phase III trial has been initiated to confirm these findings. **Methods:** TROPiCS-04 (NCT04527991) is a global, multicenter, open-label, randomized, controlled trial in patients with locally advanced unresectable or mUC who progressed after prior platinum-based and CPI therapies (with Eastern Cooperative Oncology Group performance status 0–1 and adequate hematologic, hepatic, and renal function). Patients will be randomized 1:1 to receive SG 10 mg/kg intravenously (IV) on day 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 patients deemed to be receiving clinical benefit per investigator assessment. Approximately 482 patients will be enrolled 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 v1.1), safety, and quality of life. Study initiation is ongoing and enrollment begins in Q4 2020 across ~90 sites. Clinical trial information: NCT04527991. Research Sponsor: Immunomedics, Inc.

TPS499 **Trials in Progress Poster Session**

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

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Background: Tucatinib (TUC), a highly selective HER2-directed TKI recently approved for HER2 overexpressed/amplified (HER2+) metastatic breast cancer, is being developed as a novel therapy for patients (pts) with metastatic CRC, gastric cancer, and other GI tumors. In xenograft models of HER2+ and HER2-mutated (HER2-mut) tumors, dual targeting of HER2 with TUC and trastuzumab (Tras) showed superior activity to either agent alone. Despite the development of several new therapies for metastatic urothelial cancer, response durations generally remain short and the great majority of pts succumb to the disease, highlighting the need for therapeutic approaches. Given that 20-30% of urothelial cancers have molecular alterations of the ErbB family, TUC in combination with Tras warrants further evaluation in this population. The SGNTUC-019 basket study is evaluating TUC in combination with Tras in pts with HER2+ or HER2-mut solid tumors, including a cohort of pts with locally advanced or metastatic (LAUM) urothelial cancer. **Methods:** SGNTUC-019 (NCT04579380) is a multi-cohort, open-label, international phase II study evaluating pts with previously treated solid tumors displaying HER2 overexpression/amplification or activating mutations. Eligible pts must have HER2+ or HER2-mut LAUM solid tumors, with progression on or after the last systemic therapy for advanced disease. Pts must be $\geq$18 years old, with ECOG PS $\leq$1, adequate hepatic, hematological, renal, coagulatory, and cardiac function, and no prior exposure to HER2-directed therapy. For eligibility, HER2 alterations can be demonstrated by HER2 overexpression/amplification in tumor tissue by prior IHC/ISH (IHC 3+/signal ratio $\geq$2.0 or gene copy number $>$6), or by HER2 amplification/mutation in a prior or on-study NGS assay of ctDNA or prior tissue NGS assay. The HER2 overexpression/amplification urothelial cancer cohort will enroll 12 RECIST 1.1 response-evaluable pts. If $\geq$2 responses are observed, the cohort will be expanded to a total of 30 pts. Pts with HER2-mut urothelial cancer will be enrolled in a cohort of 30 pts for all solid tumor types except breast cancer and non-squamous NSCLC. If justified, a separate cohort for HER2-mut urothelial cancer may be opened. The primary objective is antitumor activity in each cohort, with confirmed ORR as primary endpoint, and disease control rate, duration of response, PFS, and OS as secondary endpoints. Pts will receive TUC 300 mg orally twice daily and Tras 8 mg/kg IV 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 TUC will be evaluated in all pts 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 will open in the US, EU, and Asia; enrollment is anticipated to begin in Dec 2020. Clinical trial information: NCT04579380. Research Sponsor: Seattle Genetics, Inc.

TPS500 **Trials in Progress Poster Session**

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

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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 (N1-2 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 improvement of 25% in clinical CR between both arms (37.5% to 62.5%). A total accrual of 114 pts (in order to enroll 92 evaluable pts) will provide 81% power to detect this difference using a Fisher's exact test (assuming 10% drop out + anticipating that 20% chemotherapy-naïve pts will progress post IC). 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. 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, AstraZeneca for sample collection.

TPS501 **Trials in Progress Poster Session**

A phase Ib single-arm study of bintrafusp alfa for the treatment of pretreated, locally advanced/unresectable or metastatic urothelial cancer.

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Background: Urothelial cancer (UC) is the most common histological subtype of bladder cancer. For patients with metastatic UC, platinum-containing chemotherapy (CT) is the first-line standard of care. With 5 PD-(L)1 inhibitors approved for second-line treatment of platinum-refractory advanced UC, objective response rates (ORRs) in this setting (15% to 21%) and in first-line cisplatin-ineligible patients (23% to 31%) suggest that there remains a significant unmet need for improved outcomes. TGF-β signaling has been associated with resistance to PD-(L)1 inhibitors in patients with UC. Bintrafusp alfa (BA) is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. In murine models, BA resulted in improved antitumor activity vs TGF-β or PD-L1 monotherapies alone or in combination. In 2 phase I trials (NCT02517398 and NCT02699515), BA demonstrated a manageable safety profile and encouraging clinical efficacy in >670 patients with advanced solid tumors. Here we describe a phase Ib study (NCT04349280) that will assess the clinical activity and safety profile of BA in platinum-experienced patients with locally advanced/unresectable or metastatic UC. Colocalized, simultaneous inhibition of the TGF-β and PD-L1 pathways by BA is hypothesized to elicit greater antitumor activity than anti–PD-(L)1 therapies in patients with UC. **Methods:** This open-label, multicenter, single-arm trial is accruing patients with histologically confirmed locally advanced/unresectable or metastatic UC (ECOG PS ≤1) with disease progression or recurrence after platinum-based CT. Patients must not have received >2 lines of systemic therapy for metastatic disease or prior therapy targeting T-cell costimulation, or checkpoint or TGF-β pathways. Patients with pneumonitis or a history of noninfectious pneumonitis that required systemic immunosuppression are ineligible. Patients will receive BA 1200 mg every 2 weeks until progression, unacceptable toxicity, death, or study withdrawal, or for up to 2 years. The primary endpoint is investigator-assessed confirmed ORR per RECIST 1.1; key secondary endpoints include duration of response and progression-free survival per the investigator and IRC, overall survival, safety, immunogenicity, and pharmacokinetics. Exploratory biomarker analyses will be conducted using patient samples collected during screening and prior to administration of BA. The base ORR used for the null hypothesis is 21%, and the target ORR is 40%. Using a predictive probability design and an estimated enrollment of 40 patients, the type I error rate is 5.70% and the power is 85.39%. As of September 2020, 3 sites in 2 countries have been activated and no patients have been enrolled. Clinical trial information: NCT04349280. Research Sponsor: Merck KGaA, Darmstadt, Germany, and GlaxoSmithKline.

TPS503 **Trials in Progress Poster Session**

Sub-urothelial durvalumab injection-1 (SUBDUE-1): A novel approach to immunotherapy for bladder cancer.

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Background: Bladder cancer progression may be influenced by the host immunological response to the tumour. Cells strongly associated with this immunological response include Tumour Infiltrating Lymphocytes (TILs) and Tumour-Associated Macrophages (TAMs). Several solid tumours, including bladder cancer can demonstrate good responses to systemic immuno-oncology (IO) agents, however, the efficacy of IO agents in localised bladder carcinoma remains less clear, although numerous trials are underway. One such IO agent is durvalumab, an antibody against the immune checkpoint protein programmed cell death ligand 1 (PD-L1). The sub-urothelial administration of immune therapeutic agents has not been reported. This method of administrating other agents such as Botulinum toxin has shown excellent feasibility and efficacy. Local delivery could have a number of therapeutic advantages and aligns more closely with the intra-vesical therapies commonly adopted in this clinical scenario. It remains unknown whether systemic effects (both beneficial and adverse) of PD-L1 blockade would be reduced by this mode of delivery. Our aim was to establish: a protocol for the sub-urothelial administration of durvalumab. the safety and tolerability of sub-urothelial administration of durvalumab to identify an appropriate dose for future phase II studies the local immunological efficacy of sub-urothelial administration of durvalumab by assessing the quantity and distribution of TILs and TAMs in pre- and post-administration biopsies **Methods:** This dose-finding Phase Ib trial is currently recruiting patients with invasive, high-grade bladder cancer ($\geq$pT1) already scheduled for radical cystectomy. Cystoscopy under general anaesthesia and sub-urothelial injection of durvalumab will be performed a minimum of 2 weeks prior to cystectomy, utilising a 3+3 dose escalation design (25mg, 75mg, 150mg). The selected dose of durvalumab is diluted into 25mL of normal saline, and administered to the bladder using a 5Fr Bonee needle via 22Fr rigid cystoscope. PROMS, blood specimens, and tumour histopathology and immunohistochemistry at allocated times pre- and post-cystectomy are being collected for translational end-points. Analysis of safety and tolerability will be primarily descriptive in nature. This trial is registered with the Australian Clinical Trials Registry (ACTRN12620000063910, funded by ANZUP Below the Belt and has been approved by the appropriate institutional HREC. To date, four patients have been recruited. This study has a two-year recruitment target and is expected to finish recruiting in 2022. Clinical trial information: ACTRN12620000063910. Research Sponsor: Australian and New Zealand Urogenital and Prostate Cancer Trials Network, Pharmaceutical/Biotech Company.

TPS504 **Trials in Progress Poster Session**

A phase III, randomized, open-label, multicenter, global study of first-line durvalumab plus standard of care (SoC) chemotherapy and durvalumab plus tremelimumab, and SoC chemotherapy versus SoC chemotherapy alone in unresectable locally advanced or metastatic urothelial cancer (NILE).

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Background: Despite high response rates with first-Line (1L), standard, platinum-based chemotherapy (CT) (gemcitabine + cisplatin or gemcitabine + carboplatin) for patients (pts) with locally advanced or metastatic urothelial cancer (mUC), prognosis remains poor. Studies of immune checkpoint inhibitors + CT in 1L mUC have demonstrated mixed results. In IMvigor130, an improvement in progression-free survival (PFS) with atezolizumab + CT vs placebo + CT reached statistical significance, although overall survival (OS) had not reached statistical significance at the interim analysis. A subgroup analysis suggested a possible larger effect size for PFS and OS for pts with high PD-L1 expression. In KEYNOTE-361, no improvement in either PFS or OS was observed with pembrolizumab + CT vs CT alone. The combination of durvalumab (anti–PD-L1 antibody) and tremelimumab (anti–CTLA-4 antibody) has shown activity in previously treated mUC. In the DANUBE trial of 1L mUC, the co-primary endpoints were OS compared between durvalumab and CT in pts whose tumor cells and/or tumor-infiltrating immune cells express high levels of PD-L1 (≥25%) and between durvalumab + tremelimumab and CT regardless of PD-L1 expression. While neither co-primary endpoint was met, durvalumab + tremelimumab showed evidence of activity, particularly in the PD-L1–high population (hazard ratio: 0.74 [95% CI 0.59–0.93]). Collectively, these results led to an update to the NILE protocol, focusing on pts with PD-L1–high expression. **Methods:** NILE (NCT03682068) is a randomized, open-label, multicenter, phase III global trial that will randomize ~1215 previously untreated pts with histologically or cytologically documented, unresectable, locally advanced, or metastatic transitional cell carcinoma of the urothelium. Eligible pts aged ≥18 years will be randomized 1:1:1 to durvalumab + CT (Arm 1), durvalumab + tremelimumab + CT (Arm 2), or CT (Arm 3). A tumor tissue sample for biomarker analysis is mandatory as PD-L1 status is a stratification factor. The original co-primary endpoints were PFS and OS for durvalumab + CT vs CT in the intention-to-treat population. However, based on the DANUBE trial results, the primary endpoint was revised to a co-primary endpoint OS in pts with high PD-L1 expression for Arm 1 vs Arm 3 and Arm 2 vs Arm 3. Secondary endpoints will include OS, OS rate at 24 months, PFS, objective response rate, proportion of pts alive and progression free at 12 months, duration of response, disease control rate, time from randomization to second progression, health-related quality of life, and safety. Pharmacokinetics, immunogenicity, and biomarkers are exploratory endpoints. The study opened for enrollment in September 2018. Clinical trial information: NCT03682068. Research Sponsor: AstraZeneca.

TPS505 **Trials in Progress Poster Session**

A phase III, randomized, open-label, multicenter, global study of efficacy and safety of durvalumab in combination with gemcitabine plus cisplatin for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in muscle-invasive bladder cancer (NIAGARA).

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Background: Management of muscle-invasive bladder cancer (MIBC) includes both surgery and systemic therapy. Neoadjuvant cisplatin-based combination chemotherapy has demonstrated improved pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS) compared with radical cystectomy alone. Yet at least half of patients will still experience recurrence and will progress to metastatic disease. Durvalumab (anti–PD-L1 antibody) combined with gemcitabine + cisplatin, administered as either neoadjuvant or adjuvant treatment, may increase the rate of pathologic response and prolong long-term survival. This approach will be evaluated in this study in patients with MIBC identified for curable intent, as reflected in the NCCN guidelines. **Methods:** NIAGARA (NCT03732677) is a phase III, randomized, open-label, multicenter, international trial that will enroll ~1050 patients with MIBC who, prior to radical cystectomy, will be randomized (1:1) to durvalumab and gemcitabine + cisplatin (Arm 1) or gemcitabine + cisplatin (Arm 2). Following radical cystectomy, patients in Arm 1 will receive durvalumab monotherapy for 8 cycles (8 months) while patients in Arm 2 will receive no adjuvant treatment. Eligible patients are aged ≥18 years with resectable MIBC (clinical stage T2-T4aN0/1M0) with urothelial histology eligible for a radical cystectomy. Patients with pure non-transitional cell variant histologies and any small cell histology are not eligible. A tumor tissue sample for biomarker analysis is mandatory as PD-L1 expression is a stratification factor. Primary endpoints are pCR and EFS in patients with adequate renal function. Secondary and exploratory endpoints include proportion of patients who achieve pathologic response < stage II (stages Ta, T1, and carcinoma in situ) at the time of cystectomy following neoadjuvant treatment, EFS at 24 months, metastasis-free survival, efficacy of Arm 1 vs Arm 2 at radical cystectomy and proportion of patients who undergo cystectomy, OS rate at 5 years, safety, patient-reported outcomes, and pharmacokinetics. Immunogenicity and biomarkers are exploratory endpoints. Enrollment opened in Dec 2018. Clinical trial information: NCT03732677. Research Sponsor: AstraZeneca.

TPS506 **Trials in Progress Poster Session**

SURE: An open label, sequential-arm, phase II study of neoadjuvant sacituzumab govitecan (SG), and SG plus pembrolizumab (pembro) before radical cystectomy, for patients with muscle-invasive bladder cancer (MIBC) who cannot receive or refuse cisplatin-based chemotherapy.

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Background: MIBC is a systemic disease as >40% of patients (pts) ultimately develop recurrence after radical cystectomy (RC). For pts who cannot receive or refuse cisplatin-based chemotherapy there is no standard-of-care neoadjuvant therapy. Single-agent pembrolizumab, given neoadjuvantly in patients with T2-4N0M0 MIBC, documented a 42% pathologic complete response-rate (ypT0N0) in our previous trial (PURE-01, NCT02736266). However, there is a huge proportion of pts who do not benefit from single-agent immune-checkpoint inhibitors (ICI). SG is an antibody-drug conjugate (ADC) composed by a humanized anti-Trop-2 antibody, SN-38 payload (a parent compound of irinotecan), and a hydrolysable linker for SN-38 release. Based on preliminary data from TROPHY-U-01 trial, SG got fast-track designation for urothelial carcinoma (UC) by the United States Food and Drug Administration (US-FDA). In SURE trial we aim to evaluate the efficacy of neoadjuvant SG either as a single-agent (SURE-01) or combined with pembro (SURE-02), before RC.
Methods: This phase II, open-label trial will test the safety, tolerability, activity, of SG and SG+Pembro. This study will enroll pts sequentially in the 2 cohorts. Pts should have a histopathologically-confirmed predominant UC, be fit and planned for RC, have a clinical stage T2-T4N0M0 MIBC, be ineligible (Galsky criteria) or refuse to receive cisplatin-based chemotherapy. Eligible pts will receive 4 cycles of 10 mg/Kg SG IV, on days 1, 8, of each 21 day cycle (SURE-01) and SG plus Pembro on day 1, every 21 days, at the standard dose of 200 mg intravenously (SURE-02). Surgery is planned at the time of study inclusion to be performed within 2 weeks of the last dose of study drug. After surgery patients will be managed and the surgical safety data will be recorded according to the European Association of Urology (EAU) guidelines. In SURE-02, an adjuvant phase of 13 postoperative cycles of pembrolizumab will be administered. The primary endpoint of the study is to assess the proportion of ypT0N0. The total sample size of SURE is of 77 pts, distributed as 56 pts in SURE-01 and 48 in SURE-02. The assumptions include a ypT0N0 $\leq$20% as H_0 and $\geq$45% as H_1 in a single-stage A'Hern's design for SURE-01 and a 2-stage design for SURE-02 assuming a ypT0N0 $\leq$30% as H_0 and $\geq$45% as H_1. In SURE-02 a safety lead-in phase will be conducted including 10 subjects. An external Review Committee will evaluate the safety outcomes in this phase and the occurrence of pre-defined study-limiting events. Biomarker analyses will include assessment of transcriptomic clustering, immune-gene signature, next generation sequencing on tumor circulating tumor DNA (ctDNA), including single-cell RNA sequencing on frozen tumor samples, before and after treatment. Clinical trial information: 2020-004844-27. Research Sponsor: Merck; Immunomedics.

TPS507 **Trials in Progress Poster Session**

KEYNOTE-905/EV-303: Perioperative pembrolizumab or pembrolizumab plus enfortumab vedotin (EV) and cystectomy compared to cystectomy alone in cisplatin-ineligible patients with muscle-invasive bladder cancer (MIBC).

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Background: Patients with MIBC who are ineligible for neoadjuvant cisplatin-based chemotherapy receive the standard-of-care treatment of radical cystectomy (RC) and pelvic lymph node dissection (PLND); however, RC + PLND alone is associated with high rates of recurrence and relatively poor overall survival (OS). The PURE-01 study (NCT02736266) demonstrated a pathologic complete response (pCR) rate of 37% (95% CI, 28%-36%) with neoadjuvant pembrolizumab in MIBC (Necchi, Eur Urol, 2020). The combination of pembrolizumab plus EV demonstrated encouraging antitumor activity in metastatic urothelial cancer (Rosenberg, ASCO GU, 2020). KEYNOTE-905/EV-303 (NCT03924895) is a randomized, multinational phase 3 study that will assess efficacy and safety of perioperative pembrolizumab plus RC + PLND versus perioperative EV with pembrolizumab plus RC + PLDN versus RC + PLND alone for patients with MIBC. **Methods:** Approximately 836 patients will be randomly assigned 1:1:1 to 3 cycles of neoadjuvant pembrolizumab followed by RC + PLND and 14 cycles of adjuvant pembrolizumab or 3 cycles of neoadjuvant EV and pembrolizumab followed by RC+PLND and 6 cycles of adjuvant EV and pembrolizumab and then 8 cycles of adjuvant pembrolizumab or RC + PLND alone. Neoadjuvant or adjuvant pembrolizumab 200 mg will be administered intravenously every 3 weeks (Q3W). Neoadjuvant or adjuvant EV 1.25 mg/kg will be administered on days 1 and 8 Q3W. Stratification factors will be PD-L1 status (combined positive score [CPS] $\geq$10 vs $<$ 10), disease stage (T2N0 vs T3/T4N0 vs T1-T4aN1), and region (United States vs European Union vs most of the world). Adults with histologically confirmed MIBC (T2-T4aN0M0 or T1-T4aN1M0) with predominant ($\geq$50%) urothelial histology will be enrolled. These patients must also be previously untreated with systemic therapies for MIBC, be ineligible for cisplatin, have Eastern Cooperative Oncology Group performance status of 0-2, and have tumor tissue for histology and PD-L1 analysis. Imaging (CT or MRI) will be performed 5 weeks or fewer before cystectomy and at 6 weeks after cystectomy. Scans will then be performed every 12 weeks up to year 2 after cystectomy and at discontinuation. At year 3 and beyond imaging will be every 24 weeks. Coprimary end points are pCR and event-free survival (EFS) (expressing PD-L1 [CPS $\geq$10] and all patients regardless of CPS). Secondary end points are OS, disease-free survival, pathologic downstaging, safety, and patient-reported outcomes. Adverse events graded according to Common Terminology Criteria for Adverse Events v4.0 will be monitored from randomization through 30 days after last dose of study drug (90 days for serious adverse events). KEYNOTE-905/EV-303 is ongoing or planned in 25 countries across Asia, Australia, Europe, and North America. Clinical trial information: NCT03924895. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS508 **Trials in Progress Poster Session**

Pembrolizumab (pembro) plus chemoradiotherapy (CRT) versus placebo plus CRT for patients (pts) with muscle-invasive bladder cancer (MIBC): The phase III KEYNOTE-992 study.

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Background: CRT is recommended by treatment guidelines as a bladder-preserving treatment option for selected pts with MIBC. Pembro has shown clinical activity across many stages of bladder cancer (BC), including metastatic BC, MIBC, and non–MIBC (NMIBC). The interim results of 2 ongoing phase II studies (ANZUP 1502, NCT02662062; NCT02621151) evaluating the combination of pembro plus CRT are promising. The KEYNOTE-992 (NCT04241185) study will further investigate the safety and efficacy of pembro + CRT in pts with MIBC who opt for bladder preservation.
Methods: KEYNOTE-992 is a global, randomized, double-blind, placebo-controlled, multicenter phase III trial that will evaluate the efficacy and safety of pembro + CRT versus placebo + CRT in pts with previously untreated MIBC. Eligibility criteria include age ≥18 years, histologically confirmed cT2-T4a, nonmetastatic (N0M0) MIBC, and decision to pursue bladder-preserving therapy. Approximately 636 pts will be randomly assigned 1:1 to receive CRT + either pembro 400 mg IV every 6 weeks (Q6W) or placebo (pembro or placebo limited to 9 doses). The study's stratification factors are ECOG PS (0 or 1 vs 2), PD-L1 combined positive score (<10 vs ≥10), T stage (T2 vs T3 or T4), and geographic region (US vs Europe vs rest of world). The investigator must determine the CRT regimen before randomization. The following radiotherapy (RT) regimens are allowed in the trial: conventional RT consisting of 64 Gy at 2 Gy/fraction over 6.5 weeks (whole bladder with or without pelvic nodes) or hypofractionated RT consisting of 55 Gy at 2.75 Gy/fraction over 4 weeks (whole bladder only). The following radiosensitizing chemotherapy regimens are allowed: cisplatin monotherapy (35 mg/m^2 IV weekly), 5-fluorouracil (500 mg/m^2 on days 1-5 and days 22-26) + mitomycin C (12 mg/m^2 on day 1), and gemcitabine monotherapy (27 mg/m^2 IV twice weekly). Efficacy will be assessed by cystoscopy (± biopsy), CT or MRI with blinded independent central review, and by urine cytology at 10 weeks after CRT, then Q12W until the end of year 2, and Q24W thereafter. The primary end point is bladder-intact event-free survival (BI-EFS), defined as the following: time from randomization to residual/recurrent MIBC, nodal or distant metastases, radical cystectomy, or death from any cause. The key secondary end point is overall survival (OS), and additional secondary end points are metastasis-free survival, time to any NMIBC, time to cystectomy, and safety. Safety and tolerability will be evaluated using a tiered approach. Both the primary (BI-EFS) and key secondary (OS) end points will be evaluated using a stratified log-rank test, and treatment differences will be estimated using the stratified Cox proportional hazards model with Efron's tie handling method. KEYNOTE-992 is currently enrolling at sites in 19 countries globally. Clinical trial information: NCT04241185. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS509 **Trials in Progress Poster Session**

A phase I trial of chemoimmunotherapy combining bacillus Calmette-Guerin (BCG) and intravesical gemcitabine for patients with BCG-relapsing high-grade nonmuscle-invasive bladder cancer.

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Background: Intravesical BCG is the most effective treatment for high-grade non-muscle invasive bladder cancer (NMIBC), yet recurrences are common. Patients with BCG-relapsing NMIBC are often re-treated with BCG or BCG with interferon (IFN) with an expected response rate of only 40–60%. Several studies show that a major mechanism of resistance to BCG is high levels of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) in the pretreatment tumor microenvironment. Gemcitabine is a commonly used intravesical treatment for NMIBC that, in addition to direct anti-tumor cytotoxic effects, may also reduce MDSCs and Tregs. Prior trials combining BCG with intravesical mitomycin C have shown improved efficacy over BCG alone but with higher toxicity. While gemcitabine has been shown to be better tolerated than mitomycin as an intravesical treatment, no study has looked at combined BCG and intravesical gemcitabine. We hypothesize that combining BCG and intravesical gemcitabine will be well tolerated and result in higher response rates by reducing levels of MDSCs and Tregs. A novel aspect of our trial design is the use of a modified continual reassessment method to more accurately identify the maximum tolerated dose instead of the traditional 3 + 3 design used in most NMIBC phase I trials. **Methods:** This is an investigator-initiated phase I trial (NCT04179162) that will study the safety of alternating intravesical gemcitabine and BCG. Inclusion and exclusion criteria are designed so most patients who would ordinarily be re-treated with BCG or BCG/IFN would be eligible. Patients must have recurrent high-grade NMIBC within 24 months of their last BCG treatment without meeting the criteria for BCG-unresponsive NMIBC. Intravesical gemcitabine is given twice a week on weeks 1, 4, 7, and 10, for a total of 8 doses. BCG (50 mg) is given once a week on weeks 2, 3, 5, 6, 8, and 9, for a total of 6 doses. The trial is monitored using a modified continual reassessment method with increasing dose levels of gemcitabine (500 mg, 1,000 mg, 1,500 mg, and 2,000 mg) being evaluated. Adverse events are assessed using the Common Terminology Criteria for Adverse Events version 5.0. The primary objective is to determine the maximum tolerated dose of this combination to inform our planned phase II trial. Correlative studies will look at the immunomodulating effects of gemcitabine by evaluating changes in immune cell populations in serial blood and urine specimens. Tissue and urine will also be evaluated for molecular determinants of response and resistance to the combination. The trial is open to enrollment with 10 of 25 planned patients accrued to date. Clinical trial information: NCT04179162. Research Sponsor: U.S. National Institutes of HealthSupported by the Sidney Kimmel Center for Prostate and Urologic Cancers, the National Institutes of Health/National Cancer Institute to Memorial Sloan Kettering Cancer Center through the Cancer Center Support Grant, award number P30 CA008748, the Marie-Josee and Henry R. Kravis Center for Molecular Oncology, the Memorial Sloan Kettering Cancer Center Specialized Program of Research Excellence (SPORE) in Bladder Cancer P50- CA221745, the Memorial Sloan Kettering Cancer Center Bladder Cancer SPORE Career Enhancement Award, the Memorial Sloan Kettering Cancer Center Department of Surgery Faculty Research Award, the Bochner-Fleisher Scholars in Bladder Cancer Award, NIH/NCATS Grant # UL1-TR-002384, the NIH/NCI K12 Paul Calabresi Career Development Award for Clinical Oncology (K12 CA184746), and the Wofchuck Family Young Investigator Award.

Phase II/III clinical results of IL-15RαFc superagonist N-803 with BCG in BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS) patients.

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Background: Patients with NMIBC CIS unresponsive to BCG have limited treatment options. N-803 (Anktiva) is a mutant IL-15-based immunostimulatory fusion protein complex (IL-15RαFc) that promotes proliferation and activation of natural killer (NK) cells and CD8+ T cells, but not regulatory T cells. Phase Ib data in BCG-naive patients with NMIBC demonstrate that intravesical administration of N-803 with BCG induced complete response in all patients, without recurrences for the study duration of 24 months. An open-label, 3 cohort multicenter phase II/III study (QUILT 3.032) of intravesical BCG plus N-803 in patients with BCG-unresponsive high-grade NMIBC (NCT03022825) was opened. We report here the interim analysis of Cohort A, BCG-unresponsive (CIS) [with or without Ta or T1 disease], as of December 2020 data cutoff. **Methods:** All treated patients received intravesical N-803 plus BCG, consistent with the standard induction/maintenance treatment schedule. The primary endpoint for Cohort A of this phase II/III study is incidence of complete response (CR) of CIS at any time. **Results:** To date, 80 patients have enrolled in cohort A of this phase II/III trial. Evaluable analysis at this time shows CR rate at any time of 72% (N=51/71); for patients achieving CR, the probability of maintaining a CR for 12 months is 59%, with a median duration of complete response of 19.2 (7.6, 26.4) months. Low-grade treatment related AEs include dysuria, hematuria, and pollakiurua (all 16%), urgency (14%), and bladder spasm (8%), all other AEs were seen at 6% or less. A total of 9 subjects experienced at least 1 treatment emergent SAE (Severe Adverse event), the SAE rate is 1% for any given AE. No treatment emergent SAE's were considered treatment related. No immune related SAE's have been seen. To date, 10/80 (12.5%) patients proceeded to cystectomy in this BCG unresponsive population. **Conclusions:**With a CR rate of 72%, N-803 has met its primary endpoint with 59% probability of CR patients maintaining CR for at least 12 months. With the observed strong efficacy and an SAE rate of 1%, N-803 represents a novel treatment option for BCG unresponsive CIS with a favorable benefit:risk ratio, in a therapeutically challenging disease. Clinical trial information: NCT03022825. Research Sponsor: ImmunityBio.